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Editorial

Some Problems of Leprosy

THE reasons why the problems of leprosy, even today, seem almost insuperable are not far to seek. During the hundred years which have elapsed since Boeck and Danielssen's classic treatise very few facts of the disease have been settled or agreed upon by all workers; indeed almost every point is still in dispute. Thus there is yet doubt whether the bacillus of leprosy has been artificially cultivated and whether the disease has actually been transmitted to animals. The questions of communicability in man and the modes of adequate exposure are still undetermined. Therapy, even with modern drugs, remains in the stage of trial and the results are extremely difficult to appraise.

Classification. The classic monograph of Danielssen and Boeck[1] is generally accepted as the beginning of the modern study of leprosy, and like all work based on careful observation of facts it has turned out to be a most valuable contribution. Danielssen and Boeck divided cases of leprosy into the tuberculous form and the anesthetic form, the former implicating especially the skin and the latter the nerves. This classification, with its sharp differentiation of two types, has not stood the test of time but as a beginning it was useful. Hansen and Looft[2] criticized Danielssen and Boeck's "nodular" and "anesthetic" forms and suggested the terms lepra tuberosa (tuberculosa) and lepra-maculo-anesthetica be used, recognizing the fact that sooner or later nodules, macules and anesthesia are present in practically every case. The matter of classification has perhaps been needlessly overstressed in the literature; it is thoroughly discussed by Arnold,[3] and in the recent book by Chaussinaud[4] who presents the problem in the form of an elaborate table. Perhaps the difficulty has arisen in part because leprosy bacilli are so abundant and easily found in the nodular form whereas they are usually very sparse in the anesthetic form, facts which brought up the question of whether or not these varieties are really the same disease.

The Leprosy Bacillus. Gerhard Henrik Armauer Hansen, a physician of Bergen, Norway, had for years been interested in the etiology of leprosy and convinced himself that the disease was caused by some sort of bacterium. It should be recalled that at the time leprosy was universally regarded as non-contagious and was thought to be hereditary.[1] Hansen's first publication appeared in Norwegian in 1874 and an English translation was made the following year.[5] Actually this long communication deals mainly with the question of whether or not leprosy is an hereditary disease and it is not until the last page that an organism is mentioned. Hansen himself was in doubt: "There are to be found in every leprous tubercle . . . small staff-like bodies, much resembling bacteria, lying within the cells. . . . . Though unable to discover any difference between these bodies and true bacteria, I will not venture to declare them to be actually identical. Further, while it seems evident that these low forms of organic life engender some of the most acute infectious

[1] DANIELSSEN, D. C. and BOECK, W. Traité de la Spédalskhed, ou Éléphantiasis des Grecs. Paris, 1848. J. P. Baillière. [Original edition: Om Spedalskheden. Christiania, 1847.]

[2] HANSEN, G. A. and LOOFT, C. Leprosy: In Its Clinical and Pathological Aspects. Translated by Walker, N., M.D., F.R.C.P. Bristol, 1895. John Wright & Co.

[3] ARNOLD, H. L. Modern Concepts of Leprosy. Springfield, Ill., 1953.

[4] CHAUSSINAUD, R. La lèpre. 2 ed. Paris, 1955.

[5] HANSEN, G. A. I. On the etiology of leprosy. *Brit. & Foreign M.-Chir. Rev.*, 55: 459, 1875.

diseases, attributing the origin of such a chronic disease as leprosy to the apparently same matter must, of course, be attended with still greater doubts." What then was Hansen dealing with? The truth of the matter is that he was not a trained bacteriologist nor was he familiar with modern technics of cultivating and staining bacteria. Meanwhile Neisser, an expert bacteriologist, who was later to discover the gonococcus, made a trip to Norway in the summer of 1879 to study leprosy with results which he promptly reported.[6] Neisser took home tissue from lepers in which, with modern staining methods, he saw innumerable "rods." There follows a detailed description of the organisms and of their relation to the tissue cells. Niesser was unable to see bacilli in anesthetic, macroscopically undiseased skin. In a second major paper,[7] however, he straightened out the question of priority: "When I was in Bergen in July and August 1879 Hansen had the idea that rod-like structures played a role in the cause of leprosy. But even his colleagues in Bergen did not regard his findings of any importance although they had been familiar with them for years. At the time there was no question of an actual bacillus and even less of staining and culture technique. . . . I take credit, therefore, of establishing these bodies in their place as pathogenic bacteria, since I was the first who applied in exact fashion the new staining methods of Weigert and Robert Koch and brought evidence that a specific variety of bacteria is concerned in leprosy which can be brought into causal relationship with all the pathological phenomena of the disease." Neisser found the bacilli in the skin lesions, in the mucous membranes of the mouth, gums, larynx, in the interstitium of peripheral nerves, in the cornea, cartilages, testes, lymph glands, spleen and liver. The bacilli were seen inside the large "lepra cells" described by Virchow.[8]

There seems little doubt that Neisser deserves credit for going beyond the vague hypothetical stage and bringing real evidence. Who, then, should have priority for discovery of the bacillus we leave to our readers to decide. Time, however, has sanctioned the association of Hansen's name with the bacillus, and on reading Earle B. McKinley's comprehensive monograph[9] one is perplexed that the work of Neisser is not even mentioned.

Transmission to Animals. From the very discovery of the bacillus one of the questions under debate was whether or not the disease could be transmitted to animals. Neisser[7] thought perhaps he had produced leprosy in dogs although he later[10] states: "The result of all experiments to date is: Leprosy has thus far not been produced in animals." Köbner[11] tried systematically to transmit the disease to monkeys, guinea pigs, mice, rabbits, pigeons, eels and frogs, always with negative results. Hansen[12] also failed to produce lepra in a monkey. Thus the matter still stands today, according to modern reports such as those of Rogers and Muir,[13] Arnold[3] and Chaussinand.[4] At best transmission is very difficult and uncertain.

Transmission to Man. There seems no doubt that leprosy is transmitted from man to man but so high is the degree of resistance to infection that other factors such as hereditary predisposition have been invoked as essential. A modern supporter of this thesis is Aycock.[14] It is interesting that Hansen held out for the communicability of leprosy at a time when contagion was universally scoffed at and in his books[2] he treats of the matter as follows: "It is well known that the Belgian Father Damien became a leper in the Sandwich Islands. If the Father was of pure Belgian ancestry, and his disease was caused by latent hereditary bacilli, then these bacilli must have been at least several hundred years old, unless one assumes that one of his nearer ancestors had had connection with a leper, and that in this way the Father had acquired his bacilli. Against this is the explanation that the Father who tended the lepers on Molokai, with self-sacrificing love, was through some want of care or caution, infected as he went in and out

[6] Neisser, A. Ueber die Aetiologie des Aussatzes. *Jahresb. d. Schles. Gesellsch. f. vaterl. Cultur*, 57: 65, 1879.

[7] Neisser, A. Weitere Beiträge zur Aetiologie der Lepra. *Virchow's Arch. f. path. Anat.*, 84: 514, 1881.

[8] Virchow, R. Die krankhafte Geschwülste, vol. 2, p. 494. Berlin, 1864. August Hirschwald.

[9] McKinley, E. B. The etiology of leprosy. *Medicine*, 13: 377, 1934.

[10] Neisser, A. Histologische und bacteriologische Leprauntersuchungen. *Virchow's Arch. f. path. Anat.*, 103: 355, 1886.

[11] Köbner, H. Uebertragungsversuche von Lepra auf Thiere. *Virchow's Arch. f. path. Anat.*, 88: 282, 1882.

[12] Hansen, G. Studien über Bacillus leprae. *Virchow's Arch. f. path. Anat.*, 90: 542, 1892.

[13] Rogers, L. and Muir, E.: Leprosy, 3 ed. London, 1946.

[14] Aycock, W. L. Familial susceptibility as a factor in the propagation of leprosy in North America. *Internat. J. Leprosy*, 8: 137, 1940.

among the lepers. The choice between the two explanations does not seem a difficult one."

But there are grounds more relative than this. Arning[15] in Hawaii, by permission of the privy council, "was allowed to make an inoculation upon the condemned criminal Keanu, whose sentence was commuted to imprisonment for life . . . an inoculation was made of leprous matter in the convict's arm. Bacilli were found in the sore or the scar until fourteen months later, but no constitutional symptoms were observed." If correct this is a most important observation which fits in with the prevailing view that leprosy is transmitted with great difficulty. The case is questioned by Rogers and Muir[13] who say the subject "may have contracted his subsequently developing disease [leprosy] through contact with two infected relatives." Porritt and Olsen[16] more recently revised the literature on transmission by human inoculation and believed the matter was still in doubt until their observation of two U. S. Marines who were tattooed successively by the same operator on the same day. In both maculoanesthetic leprosy developed in the tattoos about two and one-half years later. "These two cases provide strong evidence for the spread of leprosy by inoculation." Interesting material on human inoculations is also to be found in the paper by Mouritz.[17]

Treatment. In no disease is therapy more difficult to evaluate. Leprosy is a disorder of remissions and relapses, and unless immediate results are obtained or unless improvement, if slow, is very marked no conclusions can be drawn. A great variety of drugs has been tried. Although Danielssen and Boeck[1] stated that "under the heading of treatment of leprosy we have little to report" they used arsenicals, iodides and potassium salts, to be sure without much enthusiasm.

However, until the introduction of the sulfones, chaulmoogra oil or related substances were the backbone of drug therapy even though the results were variously judged by different observers. Mouat,[18] in 1854, seems to have introduced the chaulmoogra into European practice from India. "The seeds yield by expression a bland fixed oil with a peculiar and slightly unpleasant smell and taste." It appears to have been known long to and prized by the natives in the treatment of leprosy. "I was first informed of its value by Mr. Jones, the Headmaster of the Hindoo college, ... at whose recommendation it was tried in the Leper Asylum, with a favorable result . . . . . it may be taken in the form of a pill, or the seed itself. . . . . In large quantity, however, it is apt to disagree, causing nausea and irritability of the stomach. A more elegant way of administering it would be in the form of the oil." The use of chaulmoogra oil and its esters is fully discussed by Sir Leonard Rogers.[19]

Faget and his associates[20] were the first to report on the effects of promine (sodium salt of p,p′-diamino-diphenyl-sulfone-N,N′-dextrose sulfonate) after Feldman, Hinshaw and Moses[21] had obtained suggestive benefits from it in experimental tuberculosis. Faget and his colleagues began their studies at the National Leprosarium at Carrville, Louisiana in 1941. The drug was given orally to a series of ten patients. Toxic reactions led to a change to the intravenous route, by which 5 gm. nearly every day for long periods was well tolerated. A slowly developing anemia is the major toxic reaction. A number of case reports are given of unselected patients who received the drug for at least twelve months. "Promine appears capable of inhibiting the progress of leprosy in a considerable percentage of cases. As yet no case of leprosy has become arrested under its influence. . . . . It is not claimed that promine is a specific for leprosy." Later Faget and Pogge[22] reported further results in the early cases. "Its action is slow and improvement usually becomes manifest after six or more months of treatment." They point out that, from the nature of the case, apparent improvement may be due to "psychological

[15] Arning. The inoculation of a condemned criminal. Editorial. *M. Rec.*, 29: 449, 1886.

[16] Porritt, R. J. and Olsen, R. E. Two simultaneous cases of leprosy developing in tattoos. *Am. J. Path.*, 23: 805, 1947.

[17] Mouritz, A. A. St. M. Human inoculation experiments in Hawaii including notes on those of Arning and of Fitch. Condensed, arranged and annotated by Wade, H. W. *Internat. J. Leprosy*, 19: 203, 1951.

[18] Mouat, F. J. Notes on Indian remedies. No. 1. The Chaulmoogra. *Indian Ann. M. Sc.*, 1: 646, 1854.

[19] Rogers, L. Recent advances in the treatment and prophylaxis of leprosy. *Edinburgh M. J.*, 37: 1, 1930.

[20] Faget, G. H., Pogge, R. C., Johansen, F. A., Duian, J. F., Prejean, B. M. and Eccles, C. G. The promin treatment of leprosy. A progress report. *Pub. Health Rep.*, 58: 1729, 1943.

[21] Feldman, W. H., Hinshaw, H. C. and Moses, H. E. The effect of promin on experimental tuberculosis. *Proc. Staff Meet., Mayo Clin.*, 15: 695, 1940.

[22] Faget, G. H. and Pogge, R. C. The therapeutic effect of promin in leprosy. *Pub. Health Rep.*, 6: 1165, 1945.

responses of patients" or to spontaneous variations in the disease. However, their photographs of patients with nodular leprosy before and after treatment are really impressive.

Diaminophenylsulfone has yielded various derivatives which have also been tried in leprosy. One of these is diasone, the disodium formaldehyde sulfoxylate. It has the advantage of being usable when given orally. Faget and Pogge[23] gave the drug a careful trial in forty-seven patients of which only three showed any advance of the disease under treatment. The toxic reactions were mild on an average dose of 1 gm. daily.

The study of various sulfone derivatives has progressed rapidly since these early studies, with as yet no final evaluation. Good brief summaries, with references, may be found in the Addendum to the third printing of Rogers and Muir,[18] in Arnold's book,[3] and in Chaussinaud's[4] (p. 233) who says (1955), "The published results have been confirmed by leprologists all over the world and at present the sulfones are considered the therapy of choice."

So there is hope of a definitive cure for leprosy, but meanwhile, as Hansen insisted in 1895,[2] "as we are, then, in our opinion, unable to destroy the bacilli with remedies, either internal or external, it only remains to us to prevent infection, and that can only be attained by isolation of those affected."

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[23] FAGET, G. H. and POGGE, R. C. The treatment of leprosy with diasone. A preliminary report. *New Orleans M. & S. J.*, 98: 145, 1945.

Clinical Studies

Wedged Hepatic Venous Pressure*

A Clinical Evaluation

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WEDGED hepatic venous pressure has been utilized to assess, indirectly, pressure in the portal venous system. To measure wedge pressure an open ended cardiac catheter is passed from an antecubital vein via the right atrium and inferior vena cava into a peripheral hepatic venule until the vessel is occluded. It is assumed that the wedged catheter dams up a static column of blood extending from the hepatic vein towards the junction of hepatic arterial and portal venous blood streams on the other side of the liver sinusoids. For the purpose of pressure measurement this has the effect of extending the catheter tip in the direction of the portal system and is analogous to the method of estimating left atrial pressure by occlusive catheterization of a pulmonary arteriole. The relationship between hepatic wedge pressure and portal venous pressure was first postulated by Myers and Taylor [*1*] and Friedman and Weiner [*2*], who made comparative measurements in animals. Myers and Taylor extended their studies to human subjects with cirrhosis, finding elevated levels of wedge pressure [*1*]. Paton, Reynolds and Sherlock [*3*], Krook [*4*] and Taylor and Myers [*5*] have confirmed these findings. Measurements on fifty-two patients with cirrhosis have been published, wedge pressure levels ranging from 11 to 50 (averaging 21.9) mm. Hg. By contrast, in a total of fifty-two patients without liver disease, wedge pressures have ranged from 0 to 11.2 mm. Hg with a mean of 6.2 mm. Hg. In the presence of extrahepatic portal hypertension, wedge pressures have been within the normal range. Elevations have been observed in congestive heart failure in the absence of cirrhosis but in this case all venous pressure levels were comparably raised and the normal small gradient between wedge pressure and right atrial pressure was not increased [*3*]. Wedge pressures were normal in a small series of patients with viral hepatitis and extrahepatic obstructive jaundice [*3*].

Portal pressure and wedge pressure were approximately equal in animals both in the resting state and after both pressures had been raised by epinephrin injection [*2*]. However, in ten cirrhotic human subjects Reynolds and coworkers [*6*] found that wedge pressure varied from 9 to 28 per cent (average 20 per cent) below portal pressure when simultaneous measurements were made at surgery. They ascribed this discrepancy to the presence of some collateral circulation preventing complete stasis of blood in the liver segment on the portal side of the obstructing catheter.

The published observations indicate that wedge pressure closely approaches portal vein pressure. They suggest that wedge pressure is elevated consistently and solely in cirrhosis, and that there are no serious technical problems inherent in its determination. The potential value of such a measurement in problems relating to portal hypertension seems obvious. However, extensive clinical application of the test has not been reported to date.

During the past three years we have utilized wedged hepatic vein pressure measurements in the clinical study of 125 patients. We have been impressed by the ease of performance and the safety of the procedure and by the frequency with which the results have been of clinical value.

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However, our original impressions regarding the specificity of wedge pressure elevations have had to be modified. Problems having to do both with the technic of making the measurement and the interpretation of the results have been encountered. The purpose of this report is to point out these problems and to illustrate the clinical situations in which wedge pressure measurements have been of value.

Recommended Method for Making the Measurement and Expressing Results. The technic of passing a cardiac catheter into the right atrium is well known and needs no description. The inferior vena cava then can be entered with relative ease if the catheter tip is directed posteriorly as it is advanced. In our experience a firm straight catheter with a curved tip has been easiest to manipulate. After reaching the inferior vena cava and rotating the catheter tip to the right and anteriorly an hepatic vein usually can be entered. Then the catheter is advanced into the liver substance until it is wedged in a peripheral hepatic venule. The pressure is noted and a continuous recording made while the catheter is withdrawn until it lies free in a larger hepatic vein. If another hepatic vein radicle can be entered the procedure is repeated. It is very helpful to the operator to know the pressures as they are being recorded. For this reason an instrument is preferred that will allow direct visual estimation of pressure in addition to a permanent record.

The renal veins or small phrenic or intercostal veins which drain directly into the vena cava might be mistaken for hepatic veins. The catheter is not likely to penetrate far into the smaller vessels and the renal vein orifices are more caudad than are those of the hepatic veins. Moreover, renal vein blood is well oxygenated and visibly brighter red than vena caval and hepatic vein blood. However, it is safest to have facilities for determination of bromsulphthalein levels available, and if there is any doubt about the origin of a vein in which pressure is being recorded bromsulphthalein can be infused intravenously and a comparison made between bromsulphthalein levels in blood drawn simultaneously from the catheter and from a peripheral artery or vein. A significant difference in concentration will verify the intrahepatic position of the catheter. If there is no significant difference it indicates either that an extrahepatic vein has been catheterized or that liver function is extremely poor.

Both right atrial and inferior vena caval pressures should be recorded at some time during the procedure. Because of the proximity of the mouth of some of the hepatic veins to the right atrium, the level of vena caval pressure may not be evident on continuous records made while withdrawing the catheter from the hepatic vein to the right atrium. It is therefore advisable to record vena caval pressure when the catheter is definitely in this vessel distal to the hepatic vein orifices.

In reporting pressures of the small magnitude involved in the liver it is essential that careful attention be paid to the zero reference point. Most investigators have measured the wedged hepatic vein pressure with the zero point at the externally estimated position of the right atrium (5 cm. posterior to the sternal angle with the patient supine) [*1,3,4*]. Since it is evident that elevations in right atrial pressure due to congestive heart failure will cause similar elevations in hepatic pressure [*3,4*], we formerly advocated using measured right atrial pressure as the zero point and expressing wedge pressure as the gradient between right atrium and wedged hepatic vein [*6*]. However, we have found that this gives misleading values when there is an increase in intra-abdominal pressure, as with tense ascites. The difference between wedge pressure and atrial pressure then reflects both hepatic resistance and the mechanical effects of the increased intra-abdominal pressure. Significant pressure gradients between right atrium and inferior vena cava have been noted in all our patients with tense ascites. For this reason we now advocate considering wedged hepatic vein pressure as the difference between the pressure level at the wedged catheter tip and the pressure in the vena cava. Wedge pressure then becomes an indication of resistance to flow through the liver and is independent of variations in intra-abdominal pressure. For example, in a patient with cirrhosis and tense ascites wedged pressure was 17 mm. Hg above vena caval pressure and 33 mm. Hg above right atrial pressure. (Fig. 1.) Seven liters of ascitic fluid were removed, leaving the hepatic vein catheter in place. The pressure gradient across the diaphragm was greatly reduced. Wedged pressure remained 17 mm. Hg above vena caval pressure but was now only 19 mm. Hg above atrial pressure.

We have considered using the pressure in a large central hepatic vein as a base line in place

of that in the vena cava. However we have observed that central hepatic vein pressures are frequently appreciably higher than vena caval pressures. Our assumption is that the catheter tip is directed against the current of blood flow in the hepatic vein and that some of the kinetic

TABLE 1
WEDGED HEPATIC VEIN PRESSURE LEVELS IN 125 PATIENTS

Type of Case	No. of Cases	Wedge Pressure (mm. Hg)	
		Mean (±S.E. mean)	Range
No intra-abdominal disease	5	3.4	2.0– 6.0
Miscellaneous non-cirrhotic abdominal disorders	7	7.0	4.0–11.0
Extrahepatic portal obstruction	4	5.5	2.0– 8.0
Cirrhosis:			
Advanced portal	86	18.4 ± 0.35	9.0–26.0
Early portal	13	9.5 ± 0.71	6.0–15.0
Miscellaneous	8	11.7 ± 1.40	6.0–19.0

energy of blood flow is being transformed into potential energy at the catheter tip and measured as pressure (Pitot effect). In the larger vena cava, where the velocity of blood flow is less, the measured pressure should approximate a true lateral pressure.

Dangers, Complications and Technical Difficulties of the Procedure. Hepatic vein catheterization appears to be perfectly safe. There are occasional instances of mild arm vein thrombophlebitis which can be minimized by the routine administration of procaine penicillin before the procedure. We formerly employed electrocardiographic control but have discontinued it since arrhythmias seldom occur if the catheter is kept away from the right ventricle and coronary sinus. Mild sedation may be given to anxious patients but is not necessary routinely.

Guiding the catheter into the hepatic vein is often more difficult in the cirrhotic than in the normal liver. Possibly because of the nodular enlargement of the liver the hepatic veins sometimes run laterally or even in a cephalad direction from their site of entry into the vena cava, making it difficult to advance the catheter into a

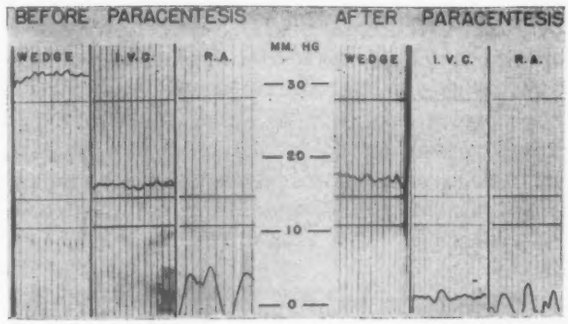

FIG. 1. Fall in right atrial—inferior vena caval pressure gradient after paracentesis in a patient with cirrhosis and ascites. The pressure gradient between wedged hepatic vein and inferior vena cava is unchanged.

wedged position. When ascites is present fluoroscopic visibility is limited and the inferior vena cava may be difficult to penetrate from the atrium, possibly because of diaphragmatic elevation. In spite of these difficulties, recording of what we have considered to be an accurate wedge pressure has been possible in approximately 90 per cent of patients.

The Normal Range of Wedge Pressure. The normal range of wedge pressure reported in the literature is from 0 to 11.2 mm. Hg above the right atrium [*1,3–5*]. Our own results in a limited number of "normal" patients suggest that wedge pressure is probably seldom more than 5 to 6 mm. Hg higher than vena caval pressures. (Table 1.) When the catheter is withdrawn from the wedged position no sudden pressure drop occurs. The values up to 11.2 mm. Hg previously reported may have been due to failure to place the zero point accurately at right atrial level or to unrecognized variations from normal in the right atrial pressure itself.

The Range of Wedge Pressure in Non-cirrhotic Diseases. Elevations in wedge pressure due to heart failure or to the mechanical effects of increased intra-abdominal pressure have been discussed previously. They will not be improperly ascribed to cirrhosis if vena caval pressure level is used as a zero reference point.

Wedge pressure levels in seven patients with miscellaneous non-cirrhotic disorders appear in Table 1. Significant pressure gradients between the wedged hepatic vein and inferior vena cava were noted in four patients. The gradients ranged from 6 to 11 mm. Hg and in each case a sudden pressure drop occurred on withdrawing the catheter from the wedged position. All of these patients had some type of disease in the abdominal cavity. The first had metastatic

ovarian carcinoma with ascites, proven at operation. The second had tuberculous peritonitis also revealed at operation. The third had hepatosplenomegaly of unknown cause. At surgery an enlarged liver with normal appearing surface was seen. Its microscopic structure looked

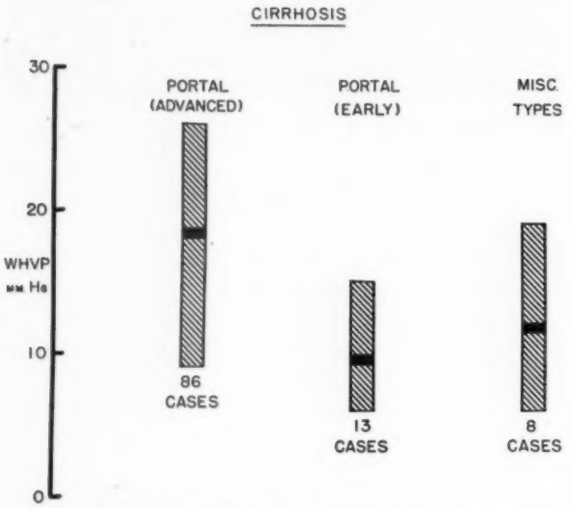

FIG. 2. Wedged hepatic vein pressure levels in various types of cirrhosis. The mean wedged hepatic vein pressure level for each group is indicated by the black bar and the range by the diagonally striped column.

normal. The portal pressure was not measured. A diagnosis was never established and the patient has since been unavailable for study. The fourth patient had a long-standing wasting febrile disease with abdominal pain and a small pulmonary infiltration. A needle biopsy specimen of the liver was interpreted as normal. He responded remarkably to streptomycin and is presumed to have had abdominal and pulmonary tuberculosis.

The elevation of wedge pressure in these patients implies an increase in vascular resistance in the liver either because of structural disease or increased volume flow. Presumably portal pressure was mildly elevated.

From the published data on wedge pressures one could conclude that significant elevations are found only in cirrhosis. However it is apparent that neither mild elevations in wedge pressure nor sudden pressure gradients between wedged and free hepatic vein can be considered to be pathognomonic of this disease.

Wedge Pressure Levels in Cirrhosis. Wedge pressure levels in 107 patients with various types of cirrhosis are illustrated in Figure 2 and listed in Table 1. The diagnosis of cirrhosis was confirmed in eighty-one cases by the microscopic examination of hepatic tissue obtained by needle biopsy or at the time of surgery or autopsy. In the twenty-six patients in whom a biopsy was not obtained the diagnosis seemed definite on the basis of clinical findings which usually included hepatosplenomegaly, spider angiomas, decreased serum albumin and increased serum globulins, either bromsulphthalein retention or icterus and, in twenty instances, ascites. The ninety-nine patients with portal cirrhosis were separated arbitrarily into "advanced" and "early" categories. A history of alcoholism was obtained in 95 per cent of this group.

The term "advanced" portal cirrhosis, as herein employed, implies the presence of symptoms referable to liver disease or the history or presence of complications such as icterus, ascites, esophageal varices or splenomegaly. With one exception all patients with advanced cirrhosis had wedge pressures of 12 mm. Hg or more above vena caval pressure. The mean wedge pressure in the group was 18.3 mm. Hg and in every patient a sudden pressure drop was noted as the catheter was withdrawn from the wedged position. The exception, with a wedge pressure of 9 mm. Hg, was asymptomatic at the time of catheterization and had a normal serum albumin level and bromsulphthalein extraction within the accepted limits of normal. However, because of the presence of hepatosplenomegaly, a microscopic picture of considerable fibrosis in the liver and a history of ascites within a year, it seemed logical to classify him as having "advanced" cirrhosis. Because of the low wedge pressure level the patient was catheterized a second time but with identical findings.

The patients with "early" portal cirrhosis had no symptoms definitely attributable to their liver disease and in most instances the sole finding was hepatomegaly with or without spider angiomas. Liver tissue was examined microscopically in all of this group and contained varying amounts of fat and some increase in fibrous tissue. The mean wedge pressure was 9.5 mm. Hg above vena caval pressure. In several cases pressures were within the normal range and there was no sudden fall in pressure on withdrawing the catheter from the wedged position.

The miscellaneous varieties of cirrhosis included primary biliary cirrhosis (four cases), hemochromatosis (one case), chronic viral hepatitis (one case), Wilson's disease (one case) and biliary cirrhosis secondary to common bile

duct stricture (one case). As might be expected wedge pressure levels varied widely in this group. None were within the normal range and abrupt gradients between wedged and free hepatic vein pressures were present in all cases.

From this wide spectrum of cirrhotic patients it is evident that wedge pressure levels may vary from normal to markedly elevated, correlating roughly with the severity of the disease. Any type of fibrotic liver disease probably may cause an elevation in wedged hepatic vein (and presumably portal vein) pressure. It seems likely that the patients with "early" cirrhosis and normal wedge pressure levels had little or no portal hypertension although we did not have an opportunity to measure portal pressure directly in any of them.

Reliability and Reproducibility of Wedge Pressure Levels in Cirrhosis. In a previous publication evidence was presented showing only minor variations between wedge pressures recorded from different hepatic vein radicles [*3*]. Taylor and Myers stated that wedge pressures measured in different areas in the liver varied by only 1 to 2 mm. Hg [*5*]. However, as our experience has broadened it has become evident that when multiple wedge pressures from different sites have been recorded, minor variations (1 to 4 mm. Hg) are frequently seen and moderate variations (5 to 7 mm. Hg) are occasionally seen. These differences could be ascribed to varying completeness of occlusion of the vein or to variations in collateral circulation. We believe that the highest pressure recorded most accurately reflects true portal pressure.

On rare occasions pressures of low magnitude have been recorded from what seemed to be a wedged position while in another, usually deeper, area in the liver a much higher pressure has been found. We have assumed that at the site of the lower pressure the catheter's advance was blocked at a venous bifurcation and true wedging in the sense of complete obstruction to the flow of blood did not occur. Unfortunately, in contrast to the situation in the lung, there is no way of making certain that the catheter is truly wedged in a hepatic venule. If penetration in the liver is deep, if blood can be aspirated only slowly from the catheter tip and if any resistance is felt on withdrawal, then true wedging is likely. However the possibility of recording an erroneously low pressure has to be considered, particularly in inexperienced hands. Obtaining wedge pressures that are in general agreement from more than one site in the liver is the best way to guard against this potential error.

On two occasions the results of hepatic vein catheterization have proved confusing. Both patients had suffered hematemeses from large radiographically demonstrated esophageal varices and both eventually proved to have cirrhosis.

The first patient, a sixty-two year old Italian man, had had a splenectomy fifteen years previously because of an enlarged spleen discovered in a physical examination. During the past two years he had vomited blood on two occasions. Evidence for cirrhosis was limited to abnormal bromsulphthalein retention. On catheterization normal wedge pressures were obtained in several veins draining the right lobe. However, when the catheter was passed into a vein approximately 7 cm. below the diaphragm leading 2 to 3 cm. to the right of the vena cava a pressure of 20 mm. Hg was recorded. The bromsulphthalein level in blood withdrawn at this site was identical with the arterial level, indicating that it was not a vein leading from functioning liver tissue. Our conclusion was that cirrhosis probably was not present. At a subsequent emergency operation for ligation of varices the liver was palpated from above and found to be grossly nodular and cirrhotic. The portal venous system was not examined. The possibility exists that the patient had cirrhosis plus a portal vein thrombosis secondary to the old splenectomy. A wedge pressure of 11 mm. Hg was reported in such a patient by Paton, Reynolds and Sherlock [*3*]. The 20 mm. Hg pressure level is the only such elevation we have encountered in a non-hepatic vein.

The second patient, a sixty-two year old Dutch woman, had had two massive hematemeses within a year. Fifteen years previously she had had a gall bladder operation followed by drainage from the incision for one year. There were no physical or laboratory evidences of cirrhosis. Wedge pressures in three different locations in the right lobe were normal. In a vein leading to the left of the vena cava, however, wedge pressure measured 16 mm. Hg above vena caval pressure. Bromsulphthalein levels in the left side vein indicated that it was, in fact, a liver vein although bromsulphthalein extraction and oxygen saturation differed markedly from the values in the right side veins. We were unable to differentiate between extrahepatic portal obstruction and hepatic cirrhosis from the catheterization findings. At surgery the left lobe of the liver appeared nodular and cirrhotic. The portal vein and the right lobe of the liver were not visualized because of dense vascular adhesions. A splenoportogram demonstrated what appeared to be normal filling of the portal vein with a few intrahepatic branches leading to the left lobe but none leading to the right. The pressure in the splenic vein was elevated and a splenorenal anastomosis was

performed. It is possible that an intrahepatic clot in the right branch of the portal vein might account for the marked difference in circulatory pattern between the two lobes but this is pure speculation on the basis of our present information.

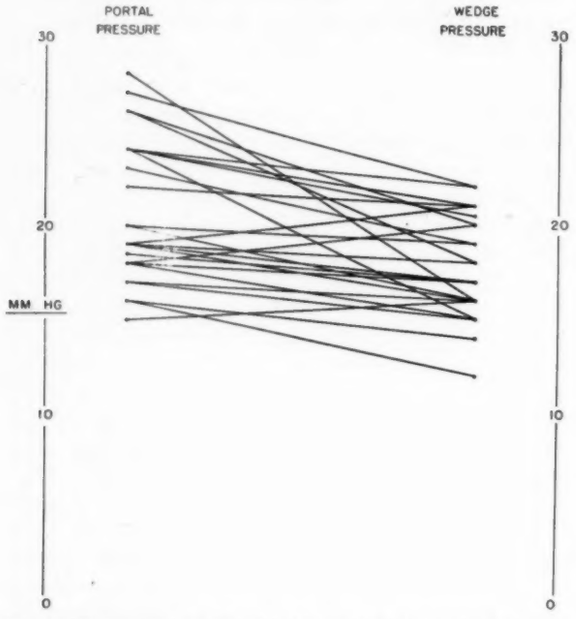

FIG. 3. Comparison of wedged hepatic vein pressure levels with portal venous system pressures measured at surgery in twenty-seven patients.

Fortunately such confusing results from hepatic vein catheterization appear to be rare but perhaps may be anticipated in patients with complex portal circulatory problems.

Comparisons between Wedge Pressure and Portal Pressure in Cirrhosis. Simultaneous comparisons between wedge pressure and portal pressure in ten patients undergoing surgery were previously reported [6]. Wedge pressure ranged from 9 to 28 per cent (mean 20 per cent) below portal pressure. There have been twenty-seven additional opportunities to compare the two pressures although none of the comparisons was simultaneous. (Fig. 3.) Portal pressure was recorded at surgery by means of a manometer (saline solution) whose zero point was placed as close to the inferior vena cava as possible. Wedge pressures were measured from a few days to as long as five months preoperatively. Because of the different recording methods used, the difficulty of obtaining a constant base line in the open abdomen and the varying periods of time between the two measurements, we believe that the results should serve only as crude data indicating that major discrepancies between wedge pressure and portal pressure are unlikely. The identical comparisons previously reported give much more exact information as to the quantitative relationship between the two pressures.

CLINICAL APPLICATIONS OF WEDGE PRESSURE MEASUREMENTS

Diagnosis of Cirrhosis. The finding of elevated wedge pressures in virtually all patients with advanced cirrhosis provides a very valuable diagnostic tool. In most instances the diagnosis of cirrhosis can be established by clinical and laboratory findings and in many of the doubtful cases needle or aspiration biopsy of the liver can be performed with little danger to the patient. However, in some instances in which confirmation of the clinical diagnosis is necessary biopsy can not be performed safely or is technically unsatisfactory. In this situation, if the proper equipment is available, measurement of hepatic wedge pressure may establish a diagnosis.

Since wedge pressures as high as 11 mm. Hg above vena caval pressure can be encountered in non-cirrhotic livers caution is indicated in the interpretation of pressures in this range. Also, it is evident that the absence of an elevated wedge pressure does not rule out an early stage of cirrhosis.

Jaundice of undetermined cause: Patient J. S., a forty-two year old Caucasian man, entered the Los Angeles County Hospital in November, 1953. He gave a history of a three weeks' episode of jaundice occurring three months previously that was diagnosed as viral hepatitis. He denied alcoholism or previous ill health. Jaundice had recurred two weeks before the present hospital admission and had increased in severity. He had eaten little during this time and lost weight. Findings on admission included mild hepatomegaly, deep icterus and a few small spider angiomas. The liver edge was mildly tender; ascites was not noted. Jaundice continued for one month, the icterus index fluctuating between 150 and 200 units. Ascitic fluid gradually appeared and the liver edge was no longer palpable. Increasing numbers of spider angiomas were seen. Laboratory work included a serum albumin of 3.2 and globulin of 3.1 gm. per 100 cc., thymol turbidity 12 units, cephalin-cholesterol flocculation test 4+, a prothrombin level of 40 per cent of normal with no response to parenteral vitamin K. Clinical opinions varied between severe progressive viral hepatitis and portal cirrhosis. A liver biopsy was deemed inadvisable because of the low prothrombin level. Hepatic vein catheterization was performed and the wedge pressure level was found to be 18 mm. Hg above vena caval

pressure, with a sudden pressure drop as the catheter was withdrawn from the wedge position. This was indicative of considerable portal hypertension making portal cirrhosis the most likely diagnosis.

The patient died two months later with hematemesis followed by hepatic coma. Autopsy revealed a typical nodular portal cirrhosis and it was subsequently learned that the patient had been an alcoholic.

Ascites of undetermined cause: Patient A. F., a seventy-four year old retired department store worker, entered the hospital complaining of painless abdominal swelling of three weeks' duration. He denied alcoholism or any episodes of jaundice. In the six months prior to the onset of abdominal swelling he had lost 20 pounds in weight which he ascribed to a reducing diet. Examination disclosed gross ascites and minimal edema of the ankles. No abdominal organs were palpated. There were no spider angiomas. Laboratory determinations were as follows: serum albumin 4.0 and globulin 1.9 gm. per 100 cc., icterus index 9 units, thymol turbidity 2 units, cephalin-cholesterol flocculation test negative, alkaline phosphatase 2 Bodansky units. There was less than 10 per cent bromsulphthalein retention forty-five minutes after an intravenous dose of 5 mg. per kg. Paracentesis revealed a whitish opaque fluid which was thought to be chylous or pseudochylous. No laboratory examinations were performed on this fluid other than a specific gravity (1.015) and a microscopic examination for malignant cells which was negative. A needle biopsy of the liver was attempted but the tissue obtained was too small in amount for adequate examination. Most observers felt that the patient had a retroperitoneal malignancy. However, hepatic vein catheterization revealed marked elevation of wedge pressure (24 mm. Hg above inferior vena caval pressure), with the abrupt drop on freeing the catheter that is characteristic of cirrhosis.

Four months later the patient died following massive hematemesis. Autopsy disclosed advanced cirrhosis and esophageal varices. No cause was found for the opaque ascitic fluid.

Assessing Candidates for Portacaval Shunt. Experience with surgical procedures for relief of portal hypertension has now extended over a sufficient number of years to establish beyond question the value of end-to-side portacaval anastomosis in the prevention of variceal bleeding. However, the operation is not one to be undertaken indiscriminately. There is a 10 to 20 per cent mortality even in selected patients [*7*]. Our own studies [*8*] and those of Bradley and co-workers [*9*] demonstrate that total liver blood flow is significantly reduced after the shunt. The hazard of ammonia intoxication may be appreciably increased [*10*]. For these reasons in recent years the operation has been limited to patients with cirrhosis who have had at least one episode of bleeding from esophageal varices and who therefore have a significant risk of another hemorrhage. Unfortunately it is not always a simple matter to establish

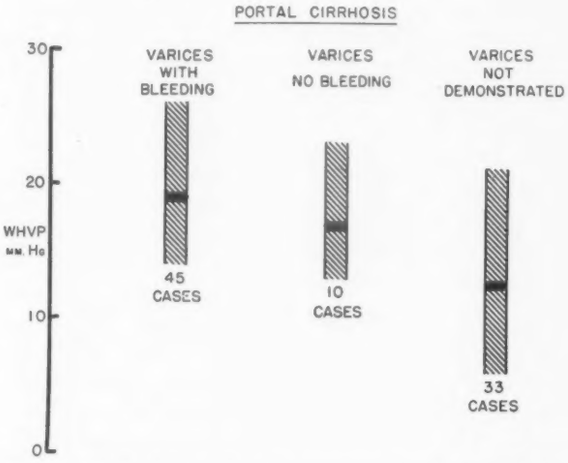

FIG. 4. Wedged hepatic vein pressure levels in patients with portal cirrhosis correlated with the presence or absence of esophageal varices. The mean and range of wedged hepatic vein pressure in each group of patients is indicated as in Figure 2.

the presence or absence of esophageal varices. In our own clinic we have had several instances both of false positive and negative roentgenologic and esophagoscopic diagnoses of varices. The occurrence of hematemesis in a patient with cirrhosis is not enough evidence on which to base a diagnosis of ruptured varices since it is well known that there is a high incidence of other potentially hemorrhagic lesions in this disease [*11*]. In this group of patients with suspected or proven cirrhosis who have suffered gastrointestinal bleeding and in whom no definite bleeding source has been demonstrated wedge hepatic vein pressure determinations have been particularly helpful. Although we have no positive evidence that rupture of varices is related to wedge pressure levels, our data do indicate that varices are more likely to be present when wedge pressure is high. This relationship is illustrated in Figure 4. Varices were considered to be present if they were demonstrated by barium swallow, esophagoscopy or autopsy or if there had been hematemesis for which the surgeon could find no other source at the time of portacaval shunt. Even allowing for possible errors in the determination of the presence or absence of

varices it seems clear that they are more likely to be present if the wedge pressure level is high. The finding of a high wedge pressure level, therefore, in a patient who has suffered hematemesis is strong evidence that esophageal varices are present and very likely the source of the bleeding. Portacaval shunt can be recommended with confidence even if varices cannot be demonstrated radiographically. Conversely, if wedge pressure is not high the likelihood that bleeding has occurred from some lesion other than varices is greatly increased. Portacaval shunt is not recommended in this situation.

Because of the mortality from the initial episode of hematemesis the indications for portacaval shunt have been broadened in some clinics to include patients with demonstrable varices that have not bled. It seems likely, although as yet undocumented, that some patients with varices may never suffer from hematemesis. In the selection of cases for "prophylactic" portacaval shunt, therefore, an important factor would be the ability to predict the likelihood of future hemorrhage. Unfortunately our data are insufficient (Fig. 4) to allow any conclusion as to the value of wedge pressure levels in this regard.

Cirrhosis, hematemesis and mildly elevated wedge pressure; bleeding probably due to peptic ulcer: Patient V. S., a thirty-seven year old Caucasian man, was hospitalized on June 30, 1954, following three episodes of hematemesis in a twelve-hour period. He gave a history of long-standing chronic alcoholic intake and of intermittent indigestion during the preceding five years. The "indigestion" was localized to the epigastric area but it was poorly described and not constantly related to meals, although definite relief had been obtained from various alkali preparations. Bleeding did not recur after the insertion of a Sengstaken-Blakemore esophageal tampon tube. Seven pints of blood were required to bring the hemoglobin level to normal. The liver edge was firm and palpable 2 inches below the costal margin. There were several tiny spider angiomas on the chest. The spleen was not felt and there was no ascites. Jaundice was noted the day after entry and persisted for six days. Laboratory findings on July 1, 1954, were serum albumin 3.4 and globulin 2.1 gm. per 100 cc., prothrombin content 100 per cent, icteric index 64 units, thymol turbidity 8 units and cephalin-cholesterol flocculation test negative. On July 1, 1954, the serum albumin was 3.1 and globulin 3.6 gm. per 100 cc., the icteric index 12 units and the thymol turbidity 3 units. Thirty minutes after the injection of bromsulphthalein (5 mg. per kg.) there was 25 per cent retention of the dye. Esophageal varices were not noted on a barium meal but the duodenal bulb was deformed and a persistent fleck of barium suggested ulcer crater. A liver biopsy specimen showed some fatty infiltration and moderate portal fibrosis consistent with alcoholic cirrhosis.

There was considerable discussion as to whether the patient had bled from esophageal varices or from a duodenal ulcer and there was a difference of opinion as to whether a portacaval shunt was indicated. Hepatic vein catheterization was performed on July 28, 1954. Wedge pressure was only mildly elevated (11 mm. Hg above vena caval pressure) although the abrupt pressure drop characteristic of cirrhosis was seen as the catheter was withdrawn from the wedged position. With these findings it seemed unlikely that any marked degree of portal hypertension was present and conservative therapy was elected.

The indigestion cleared completely when routine ulcer management was instituted. On August 23, 1954, the liver edge was still palpable and firm, the serum albumin level was 4.6 and the globulin 2.6 gm. per 100 cc. and bromsulphthalein retention was less than ten per cent thirty minutes after a dose of 5 mg. per kg. There has been no recurrence of hematemesis to date.

Cirrhosis, hematemesis and elevated wedge pressure; bleeding from esophageal varices: Patient L. B., a sixty-one year old Caucasian woman, gave a history of repeated episodes of hematemesis requiring blood transfusions since 1944. Numerous x-ray studies of the esophagus and stomach were said not to have revealed a source for the bleeding. In 1948 the spleen had been removed following one of the episodes. In 1951 surgery was again performed after a questionable duodenal ulcer was demonstrated on x-ray. At surgery no ulcer or bleeding source was identified but a nodular cirrhotic liver was noted. Intermittent hematemesis continued and on June 11, 1954, she was admitted to the Los Angeles County Hospital during one such episode. The liver edge was palpable 2 cm. below the costal margin on inspiration; there were no other physical evidences of cirrhosis. There was no history of alcoholism. Laboratory tests included serum albumin 3.0 and globulin 2.4 gm. per 100 cc., icterus index 7 units, thymol turbidity 6 units, cephalin-cholesterol flocculation test 2+, prothrombin time 70 per cent of normal and bromsulphthalein retention of 27 per cent thirty minutes after administration of 5 mg. per kg. Upper gastrointestinal x-ray study was done twice and was interpreted as showing probable esophageal varices, a deformed duodenal bulb and a questionable abnormality in the greater curvature of the body of the stomach. Esophagoscopy and gastroscopy were performed and varices were not seen. The endoscopist felt that hypertrophic rugae in the stomach and lower esophagus were responsible for the x-ray changes.

Medical opinion was divided as to the source of the patient's bleeding. Some felt that an attempt at a portacaval shunt was indicated while others believed that intensive peptic ulcer management was the

procedure of choice. Hepatic vein catheterization was performed revealing a wedged hepatic venous pressure 17 mm. Hg above vena caval pressure, falling abruptly when the catheter was withdrawn. With this evidence of considerable portal hypertension it was felt that the source of the patient's hemorrhages was probably varices and a portacaval shunt was attempted. Marked vascular adhesions were encountered in the upper abdomen and because of her poor condition the attempt was abandoned.

Two weeks later another large hematemesis occurred and was followed by hepatic coma and death. Autopsy findings included an 800 gm. cirrhotic liver, multiple esophageal and gastric varices with a visible bleeding point in the esophagus and a small stellate scar on the greater curvature of the stomach that was thought to represent a healed ulcer. There was no abnormality in the duodenum.

Differentiation between Intrahepatic and Extrahepatic Portal Block. If, in a patient who has had gastrointestinal bleeding, the diagnosis of cirrhosis is firmly established and varices are definitely demonstrable esophagoscopically or by x-ray then wedge pressure determination is superfluous. However, if there is any question about the presence of cirrhosis, wedge pressure measurement is a reliable method of determining whether the varices are due to intrahepatic or extrahepatic disease. In extrahepatic portal block wedge pressure is within the normal range. Our own experience included only four such cases verified at surgery or autopsy but a total of fourteen, all with normal wedge pressures, have been described in the literature [*3,5*].

Patient W. T., a sixty year old Caucasian man, was first seen in 1947 when a diagnosis of cirrhosis was made because of a palpable liver edge and a history of prolonged alcoholism. He was seen again in 1951 at which time the liver edge was said to be four fingerbreadths below the right costal margin, serum albumin and globulin levels were 3.7 and 1.6 gm. per 100 cc. and there was 15 per cent bromsulphthalein retention forty-five minutes after the administration of 5 mg. per kg. During the latter part of 1951 he had a severe bout of pancreatitis. In August, 1953, a serious hematemesis occurred which subsided immediately upon insertion of an esophageal tampon tube. The spleen was now definitely enlarged and the liver edge was palpable just below the costal margin. Roentgenologic examination of the esophagus and stomach suggested varices in the lower esophagus and possibly in the upper stomach. Serum albumin and globulin were 3.9 and 1.9 gm. per 100 cc., thymol turbidity was 3 units and bromsulphthalein retention was 10 per cent in thirty minutes. A diagnosis of cirrhosis with portal hypertension was made in spite of the relatively normal bromsulphthalein excretion and lack of accessory signs of cirrhosis. Wedged hepatic vein pressure was measured and found to be only 6 mm. Hg above vena caval pressure. There was no sudden fall in pressure when the catheter was withdrawn from the wedged position. These findings indicated either an extrahepatic portal obstruction or some bleeding source other than varices. At operation the splenic vein was found to be thrombosed in an inflammatory mass which included the pancreas, there was extensive collateral circulation between an enlarged spleen and the greater curvature of the stomach, and there were numerous gastric and lower esophageal varices. The liver looked normal grossly and microscopically and portal vein pressure was within normal limits.

SUMMARY

The measurement of wedged hepatic venous pressure can be accomplished in approximately 90 per cent of patients and is without danger in experienced hands. From it a reliable estimate of portal vein pressure can be made. If inferior vena caval pressure is used as a zero reference point, non-cirrhotic ascites and right heart failure do not cause elevations of wedge pressure. Moderate and marked elevations are seen only in fibrotic liver disease, although mild elevations have been found in patients with no evidence of liver disease. In the earlier stages of cirrhosis wedge pressure may be normal, therefore in the lower pressure ranges neither the presence or absence of elevated wedge pressure can be considered diagnostic with respect to cirrhosis.

The chief technical problem in wedge pressure measurement is that there is no safeguard in inexperienced hands against the recording of a falsely low pressure when the catheter is caught at a venous bifurcation and incompletely wedged. Therefore it is recommended that wedge pressure be recorded in at least two areas in the liver. There are rare instances (in our experience always in patients with complicated intra-abdominal circulatory problems) where wedge pressures may be difficult or impossible to interpret properly.

Wedge pressure determination has proved to be of practical clinical value in several circumstances. It may establish a definite diagnosis of cirrhosis in problem cases in which liver biopsy is hazardous or technically not satisfactory. In patients with known cirrhosis who have had gastrointestinal bleeding from an unknown source it will provide important evidence in favor of or against construction of a

portacaval shunt. It will differentiate reliably between intrahepatic and extrahepatic portal obstruction in patients with known esophageal varices.

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Chlorpromazine Jaundice*

Analysis of Twenty-two Cases

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SINCE the early reports in 1954 of jaundice as a side effect of chlorpromazine therapy an extensive literature has been published on the subject. However, there is some divergence of opinion regarding the clinical picture, the nature of the associated liver injury and the pathogenesis. Diffuse hepatitis and cirrhosis [*1*], hepatic necrosis [*2*] and death subsequent to liver damage [*2–4*] have all been attributed to the use of chlorpromazine. There is also a difference of opinion as to the role of previous liver disease in predisposing to the occurrence of chlorpromazine jaundice [*1,2,5,6*].

During a fourteen-month period, starting January 1, 1955, we have encountered twenty-seven patients who became jaundiced during or after chlorpromazine administration and were admitted to The Mount Sinai Hospital for study. Of the twenty-seven patients, five have been excluded from this series because of insufficient clinical or laboratory data for unequivocal diagnosis. The clinical course, laboratory abnormalities and pathologic features of the remaining twenty-two patients have been uniform and seem consistent with the concept that chlorpromazine jaundice represents a distinct syndrome, the main feature of which is intrahepatic biliary tract obstruction.

ANALYSIS OF CASES

A summary of the pertinent data of the twenty-two patients used for this analysis appears in Table 1. There were nine men and thirteen women; all were Caucasian except one Negro woman. The average age was forty-nine years with a range from twenty-six to seventy-five. Seventeen patients were given chlorpromazine for psychiatric reasons, three of these with gastrointestinal symptomatology. The others received the drug for pruritus, hiccoughs, post-radiation vomiting, nausea following broad-spectrum antibiotic therapy, and for the pain of lung abscess, respectively.

The total dose of chlorpromazine and the duration of therapy were determined fairly accurately in nineteen cases. The average total dose was 1,260 mg. taken orally over an average of fifteen days, the smallest total dose being 10 mg.

Systemic symptoms preceding or coincident with the onset of jaundice were evident in twenty of the twenty-two patients, the onset of this prodrome occurring on the average fourteen days after the first chlorpromazine tablet, with a range of six to forty-two days. The upper limit of forty-two days was exceptional in that the next longest period was twenty-five days.

The prodrome consisted of few or multiple symptoms, but fever was common to at least fifteen patients. Eight patients gave a history of chills and twelve complained of mild or moderate abdominal pain, usually epigastric or right upper quadrant pain, occasionally radiating to the back. Nausea was prominent in five patients, vomiting in five, myalgias in three, lassitude in four, constipation in two and diarrhea in one. In one patient a transient maculopapular eruption developed during the prodrome. Two gave histories of moderate weight loss. Pruritus began prior to the onset of icterus and coincident with the prodrome in eight patients and in an additional five when the jaundice appeared. The average duration of the prodrome, as limited by the onset of jaundice or the cessation of fever, when present, was 4.5 days, with a range of one to eleven days. In seven patients the first evidence of jaundice coincided with the onset of fever or abdominal pain. The average interval to onset of jaundice, as dated from the first dose of chlorpromazine, was 18.6 days.

When the patients were first seen by us, thirteen were moderately icteric, six were minimally

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TABLE I

TABULAR SUMMARY OF TWENTY-TWO CASES OF CHLORPROMAZINE JAUNDICE

Case, Age, Race, Sex	Date of First Dose	Total Dose (mg.)	Prodrome			Date of Onset of Jaundice	Laboratory Findings*										Duration of Jaundice (days)	Remarks
			Interval from Day of First Dose (days)	Duration (days)	Symptoms		Date	T. S. B. (mg. %)	A. P. (K.-A. units)	Ch. (mg. %)	Ch. E. (mg. %)	C. C. F.	A./G. (gm. %)	% Eos.	U. B.	U. U.		
Case 1: 75 yr., white, female	2/24/55	525 over 7 days	8	2	Pruritus	3/6/55	4/1/55	14	17.8	340	236	0	4/3.1	3	3+	1:20	80	Surgery contemplated; 5/2/55 gall bladder series negative; gastrointestinal series negative; liver biopsy
							4/7/55	11	17.1	260	186	0	.....	..	3+	1:40		
							4/14/55	8.2	13.8	322	227	0	.....	..	1+	1:80		
							4/19/55	7.8	20.6	290	190	0	.....	..	1+	1:20		
							4/25/55	5	13.8	...	...	0	.....	7	....	.....		
							5/2/55	3.6	12.1	...	...	0	.....	..	Tr.†	1:20		
							5/13/55	2.2	14.6	344	306	0	4.1/3.2	..	Tr.	1:10		
							5/20/55	1.3	8.0	...	...	0	.....	..	....	.....		
							5/31/55	0.9	....	...	...	.....	.....	..	....	.....		
Case 2: 57 yr., white, female	9/14/55	75 over 7 days	20	3	Fever, pruritus, abdominal pain	10/6/55	10/8/55	6.5	18.5	256	170	0	4.2/3.1	1	4+	0	43	10/25/55 gall bladder series negative; gastrointestinal series negative; liver biopsy
							10/12/55	7.4	14.0	295	221	0	3.7/3.7	0	1+	1:5		
							10/19/55	5.6	12.2	...	...	0	3.5/3.4	..	Tr.	1:20		
							10/25/55	3.1	11.8	...	...	.....	4/2.9	..	0	1:40		
							10/31/55	3.0	....	270	206	.....	3.8/3.1	..	....	.....		
							11/7/55	1.6	8.9	255	190	0	.....	..	0	1:10		
							11/14/55	1.2	9.4	192	152	0	3.8/3.1	..	....	.....		
							12/5/55	0.6	7.9	220	...	.....	.....	..	....	.....		
Case 3: 33 yr., white, female	10/22/55	1,515 over 6 days	12	5	Fever, myalgias	.....	11/4/55	.....	....	...	...	.....	.....	8	....	.....	.....	Grippe-like syndrome; no clinical jaundice; 12/20/55 gall bladder series negative
							11/5/55	.....	....	...	...	.....	.....	5	....	.....		
							11/8/55	1.1	20.9	...	...	0	4.1/2.9	..	...	.....		
							11/18/55	0.4	10.3	...	...	0	4.6/3.1	..	...	.....		
Case 4: 26 yr., Negro female	11/16/55	1,750 over 21 days	7	11	Fever, pruritus, chills	12/4/55	12/8/55	12.4	36.3	385	288	0	5.3/2.4	4	4+	0	30+	12/30/55 gall bladder series negative; liver biopsy
							12/15/55	9.1	25.6	330	265	0	4/3.6	6	1+	1:10		
							12/21/55	6.1	30.4	336	250	0	3.8/3.8	..	0	1:10		
							12/28/55	3.8	19.4	304	227	0	3.8/3.2	..	....	.....		
							2/15/56	0.7	7.7	200	...	0	.....	..	....	.....		
Case 5: 38 yr., white, male	6/26/55	5,700 over 57 days	42	10	Pruritus, abdominal pain, vomiting	8/18/55	8/25/55	2.9	15.8	265	206	0	3.5/2.6	16	0	1:120	7	Gastrointestinal series negative
							8/30/55	.....	....	...	...	.....	.....	..	0	1:20		
							10/14/55	.....	6.5	...	...	.....	.....	..	....	.....		
Case 6: 27 yr., white, female	7/2/55	150 over 6 days	16	3	Fever, pruritus, chills, abdominal pain	7/21/55	7/21/55	2.1	....	...	...	.....	.....	..	...	.....	30	7/27/55 gall bladder series no visualization; 8/24/55 gall bladder series negative; gastrointestinal series negative; liver biopsy
							7/23/55	5.0	29.6	245	160	1+	3.9/3.4	20	0	1:20		
							8/1/55	6.2	28.8	210	170	1+	3.2/3.4	4	0	1:40		
							8/9/55	2.5	26	205	139	0	4/3.1	9	0	1:40		
							8/16/55	1.9	19	208	160	0	.....	..	....	.....		
							8/23/55	.....	12.5	...	...	.....	.....	..	....	.....		

Case 7: 59 yr., white, female	5/10/55	1,050 over 21 days	22	7	Fever, pruritus, abdominal pain	6/5/55	6/8/55	11.2	16.6	378	290	0	4.3/3.1	3	2+	1:20	35	6/25/55 gall bladder series negative; gastrointestinial series negative; liver biopsy
							6/16/55	7.0	17.9	325	235	0	3.7/3.3	..	0	1:20		
							6/23/55	2.7	16	332	234	.....	3.6/2.6	..	....	.....		
							6/29/55	2.5	23.5	342	327	0	3.8/3.6	..	0	1:40		
							7/8/55	1.4	16.2	...	...	0	.....	..	....	.....		
Case 8: 29 yr., white, female	2/15/55	500 over 5 days	9	4	Pruritus, chills, abdominal pain, vomiting	2/28/55	2/28/55	2.1	5.0	260	...	0	.....	2	4+	.....	122	11/15/55 gall bladder series negative
							3/4/55	8.4	14.4	315	225	0	4.4/2.5	..	4+	1:10		
							3/9/55	10.0	13.3	300	...	0	3.7/3.4	..	3+	1:40		
							4/15/55	7.6	....	...	...	.....	.....	..	....	.....		
							5/15/55	5.3	....	...	...	.....	.....	..	....	.....		
							6/6/55	1.2	....	...	...	.....	.....	..	....	.....		
							11/15/55	0.55	....	240	204	0	4.7/2.9	..	....	.....		
Case 9: 45 yr., white, male	1/7/55	825 over 11 days	11	2	Fever, chills, vomiting	1/18/55	1/21/55	5.6	27.8	215	150	1.2‡	.....	7	2+	1:20	16	Gastrointestinal series negative
							1/26/55	4.9	31	...	...	2+	.....	..	....	.....		
							1/31/55	2.0	27.2	...	...	0	.....	..	0	1:60		
							7/7/55	.....	12.7	...	...	0	3.7/3.2	..	....	.....		
Case 10: 48 yr., white, female	11/17/55	950 over 18 days	9	5	Fever, pruritus, chills, abdominal pain, vomiting, myalgias	12/1/55	12/8/55	8§	11¶	240	...	0	.....	..	Tr.	1:2	16	12/20/55 gall bladder series negative; liver not palpable
							12/15/55	1.3	15.6	270	163	0	3.8/3.8	0	0	1:16		
							12/16/55	.....	....	...	...	.....	.....	2	0	1:20		
							1/3/56	8.4§	3.0¶	...	...	.....	.....	..	....	.....		
Case 11: 42 yr., white, male	11/5/55	3,500 over 20 days	25	5	Fever, pruritus, abdominal pain, vomiting	12/3/55	12/2/55	0.4	....	...	...	.....	4.3/2.9	19	...	.....	9	.....
							12/3/55	.....	....	...	...	.....	.....	..	4+	1:40		
							12/5/55	4.0	28	...	...	0	.....	10	....	.....		
							12/8/55	0.87	30.4	232	134	0	4.6/2.5	..	....	.....		
Case 12: 60 yr., white, female	10/29/55	900 over 12 days	11	2	Pruritus, abdominal pain	11/10/55	11/30/55	14.8	28	372	261	0	4/3.5	..	Tr.	1:20	90	Gastrointestinal series negative
							12/4/55	10	25	...	...	.....	.....	..	4+	1:80		
							12/7/55	.....	....	...	...	.....	.....	..	4+	1:40		
							2/13/56	1.2	....	...	...	.....	.....	..	....	.....		
Case 13: 66 yr., white, male	10/12/55	500 over 20 days	..	..	Pruritus	11/2/55	11/7/55	3.4	23.1	350	255	0	4/3.2	8	Tr.	1:80	14	No systemic symptoms; gastrointestinal series negative
							11/13/55	1.9	17.2	...	...	.....	.....	..	0	1:20		
Case 14: 61 yr., white, male	?	? over 21–35 days	?	?	Chills, abdominal pain	9/29/55	10/3/55	7.6	32.3	...	...	0	.....	5	1+	1:80	19	10/6/55 gall bladder series negative; gastrointestinal series negative; liver not palpable
							10/7/55	5	30	...	...	.....	.....	..	Tr.	1:40		
							10/12/55	2.4	....	...	...	.....	.....	..	0	1:20		
Case 15: 44 yr., white, male	?	?	?	3	Fever, chills, abdominal pain	10/1/55	10/1/55	.....	....	...	...	.....	.....	15	0	1:20	20	ACTH 10/7/55–10/12/55
							10/3/55	8.4	34.9	...	...	0	.....	17	....	.....		
							10/10/55	5.2	....	...	...	.....	.....	..	...	.....		
							10/14/55	2.4	20.2	...	...	.....	.....	..	....	.....		

* T. S. B.: total serum bilirubin.
A. P.: serum alkaline phosphatase (in King-Armstrong units).
Ch.: total serum cholesterol.
Ch. E.: serum cholesterol esters.
C. C. F.: cephalin-cholesterol flocculation reaction.
A./G.: serum albumin/serum globulin.
% Eos: per cent of eosinophils in peripheral blood smear.
U. B.: urine bile.
U. U.: urine urobilinogen.
† Tr.: trace.
‡ Thymol turbidity.
§ Icterus index.
¶ Bodansky units.

TABLE I (*Continued*)

TABULAR SUMMARY OF TWENTY-TWO CASES OF CHLORPROMAZINE JAUNDICE

Case, Age, Race, Sex	Date of First Dose	Total Dose (mg.)	Prodrome: Interval from Day of First Dose (days)	Prodrome: Duration (days)	Prodrome: Symptoms	Date of Onset of Jaundice	Laboratory Findings*: Date	T. S. B. (mg. %)	A. P. (K.-A. units)	Ch. (mg. %)	Ch. E. (mg. %)	C. C. F.	A./G. (gm. %)	% Eos.	U. B.	U. U.	Duration of Jaundice (days)	Remarks
Case 16: 62 yr., white, female	?	?	?	4	Pruritus, chills, abdominal pain	2/10/55	2/11/55	11	42.6	406	262	0	3.8/3.2	..	4+	1:10	30	Cholecystectomy 7 yr. before, common duct free of stones; 2/14/55 intravenous cholangiogram negative; liver not palpable
							2/17/55	2.7	31.5	...	...	.....	.....	..	Tr.	1:40		
							2/21/55	.....	....	...	...	0	.....	..	0	1:5		
							2/23/55	1.4	23.6	...	...	.....	.....	..	0	1:5		
							3/18/55	0.8	....	...	...	.....	.....	..	....	.....		
Case 17: 39 yr., white, male	2/12/55	525 over 7 days	20	?	Fever	3/11/55	3/11/55	7.4	19.6	...	...	.....	4.1/2.6	26	....	.....	60	.....
							3/14/55	.....	....	...	...	0	.....	..	0	1:10		
							3/16/55	6.2	21.3	...	...	0	.....	0	1+	1:20		
							4/4/55	4.1	23.7	...	...	0	.....	..	....	.....		
							4/22/55	1.7	30	...	...	.....	.....	..	....	.....		
Case 18: 53 yr., white, male	8/?/55	700 over 14 days	14	4	Fever, myalgias	.....	.....	.....	.....	...	...	.....	.....	..	....	.....	.....	First course
	1/27/56	10 one dose	1	1	Abdominal pain, back pain	1/30/56	1/31/56	2.5	22.2	254	198	0	4.4/2.8	4	1+	1:40	14	Second course—accelerated reaction following reinstitution of therapy; 2/6/56 gall bladder series negative
							2/3/56	1.5	13.1	200	...	.....	4.3/3.2	..	....	.....		
							2/10/56	0.9	....	210	...	0	3.9/2.7	..	0	1:20		
Case 19: 54 yr., white, female	1/31/56	1,650 over 13 days	9	7	Fever, maculopapular rash	2/13/56	1/25/56	.....	.....	240	...	.....	.....	1	....	.....	15	2/13/56 white blood cells 3,200 per cu. mm.; 2/17/56 Rumpel-Leede positive
							2/14/56	2.5	34.7	...	...	.....	.....	..	2+	.....	.....	
							2/16/56	.....	33.8	195	135	0	3.3/2.2	3	2+	1:40	.....	
							2/24/56	1.3	27	266	201	.....	3.0/2.9	..	4+	1:20	.....	
Case 20: 51 yr., white, female	10/19/55	525 over 7 days	8	Few	Fever, pruritus, diarrhea	10/26/55	12/9/55	3.8	....	...	...	.....	.....	..	Tr.	1:10	77+	12/23/55 gall bladder series negative; gastrointestinal series negative
							12/17/55	4.2	19.4	330	270	0	3.7/3.0	..	Tr.	1:20		
							12/21/55	.....	....	...	...	.....	.....	..	3+	1:80		
							12/24/55	5.2	19.1	340	260	0	.....	..	Tr.	1:80		
							12/30/55	5.3	18.4	...	...	0	.....	..	Tr.	1:10		
							1/5/56	3.6	14.6	264	190	0	.....	..	....	.....		
							1/10/56	3.8	14.3	...	...	0	.....	..	Tr.	1:40		
							2/8/56	1.7	7.3	...	...	.....	.....	..	Tr.	.....		
							3/7/56	0.8	....	...	...	.....	.....	..	Tr.	.....		
Case 21: 62 yr., white, female	11/1/55	1,300 over 13 days	13	1	Fever, chills	.....	11/13/55	.....	....	...	...	.....	.....	4	0	1:20	.....	Gall bladder series and gastrointestinal series negative prior to admission; intramuscular chlorpromazine on 11/15/55 without apparent exacerbation of symptoms
							11/14/55	0.45	32.2	...	...	0	.....	..	0	1:20		
							11/18/55	0.19	17.6	...	...	0	.....	..	0	1:20		
							12/7/55	.....	....	...	...	.....	.....	2	....	.....		
Case 22: 56 yr., white, male	2/26/55	1,350 over 19 days	6	5	Fever	3/8/55	2/24/55	.....	10.9	234	195	.....	.....	3	....	.....	21+	3/18/55 surgical exploration and liver biopsy
							3/9/55	.....	36.4	...	...	0	.....	..	2+	1:20		
							3/14/55	8.6	....	...	...	.....	.....	2	....	.....		
							3/24/55	4.4	....	...	...	.....	.....	..	....	.....		
							3/28/55	2.5	....	...	...	.....	.....	3	....	.....		
							5/9/55	.....	....	...	...	.....	.....	6	....	.....		
							5/16/55	.....	....	...	...	.....	.....	8	....	.....		

icteric and one patient was deeply icteric. Two patients were anicteric throughout their illness; one of these (Case 3) will subsequently be described in more detail. The liver was palpable in eighteen; in none was it felt lower than 4 cm. below the right costal margin. The liver was slightly tender in five, and in two others there was epigastric tenderness. The finding of tenderness was difficult to evaluate, however, in those patients who suffered from psychiatric disorders. In none of the twenty-two was the spleen palpable. No other significantly contributing physical findings were noted.

At the time of admission the diagnosis of chlorpromazine jaundice was made outright in seven patients and listed as preferred in another six. In two each the initial diagnostic impression was infectious hepatitis and choledocholithiasis; and in three carcinoma of the head of the pancreas was favored initially. Of the two patients who remained anicteric, the "grippe" was suspected in one and pyelonephritis in another.

The erythrocyte sedimentation rate ranged from 4 mm. per hour to 52 mm. per hour. A 3+ or 4+ guaiac reaction was obtained in the stools of four patients but was only transient. In one patient (Case 19), who was treated with chlorpromazine in the hospital for severe agitation, the white blood count fell to 3,200 per cu. mm. coincident with the onset of jaundice, and a Rumpel-Leede test was positive. Fortunately, the white count rose within a week and there were no manifestations of bleeding.

The highest serum bilirubin recorded during the hospital admissions of the twenty-two patients was 14.8 mg. per cent. In twenty the cephalin flocculation test was negative after twenty-four and forty-eight hours; in two the cephalin flocculation test was transiently 1+ and 2+, respectively. The highest serum alkaline phosphatase observed was 36.4 King-Armstrong units. The alkaline phosphatase was elevated in all patients except one (Case 8), and in that instance it rose from 5 King-Armstrong units to 14.4 King-Armstrong units four days after admission. The total serum cholesterol was greater than 300 mg. per cent in eight of the sixteen patients when the value was recorded. The highest serum cholesterol was 406 mg. per cent. In almost all instances the cholesterol esters were proportionately elevated. The serum total protein and serum albumin and globulin were normal in eighteen cases in which the values were recorded. The prothrombin time was normal in the fifteen cases in which it was determined. Urobilinogen was initially absent from the urine in only two cases. A white cell differential count was performed at least once in seventeen patients, and fourteen had 3 per cent eosinophils or more. Eight patients had 7 per cent eosinophils or greater, the highest recorded value was 26 per cent.

Oral cholecystography was performed in eleven patients, with adequate visualization of the gall bladder and without the demonstration of stones. An additional patient, who had had a cholecystectomy performed seven years previously, had a completely normal choledochography with intravenous cholografin.® Nine patients had upper gastrointestinal barium x-ray studies which revealed no abnormality; these included four who did not have x-rays of the gall bladder. One patient (Case 22) was explored on the eleventh day of jaundice, and at that time the liver was found to be enlarged and of rubbery consistency; the common bile duct and gall bladder appeared normal. The assisting surgeon was of the opinion that there was some induration of the pancreas. Liver biopsy in this case showed a marked eosinophilic periportal cellular infiltrate and central-lobular bile stasis, to be described in detail subsequently.

The duration of jaundice varied greatly. Two patients remained anicteric, although in one of these (Case 3) the serum bilirubin was initially recorded as 1.1 mg. per cent. Of the twenty who were clinically jaundiced, the shortest duration of jaundice was seven days and the longest was 122 days, with a mean of thirty days. In all cases the course was uncomplicated (except for exploratory surgery in one) and in no instance was there clinical or laboratory evidence of residual liver damage or cirrhosis.

ILLUSTRATIVE CASE HISTORIES

CASE 4. The details of this case illustrate the typical findings in this series. (Table I.)

L. B., a twenty-six year old married Negro woman, began oral chlorpromazine therapy, 75 mg. per day, on November 6, 1955, for the symptoms of a reactive depression. On November 23 she noted the onset of generalized pruritus and on November 30 chilly sensations and a fever as high as 102.6°F. developed, which persisted for two days. She complained of constipation for a few days and this was followed by nausea and several episodes of vomiting. When the temperature fell to normal on December 2, 1955, dark orange urine and grey stools were first noted. On December 5, she

was seen again by her psychiatrist and the chlorpromazine was discontinued.

On December 8 the patient was admitted to The Mount Sinai Hospital complaining of jaundice and pruritus. She was afebrile. There was moderate icterus of the skin and scleras. The liver was palpable 3 cm. below the right costal margin and was non-tender. The laboratory findings on this day (Table 1) were those usually obtained in obstructive jaundice. The white blood count was 8,200 per cu. mm. and a differential count revealed 4 per cent eosinophils. On December 9 a needle biopsy of the liver was performed and the specimen showed cholestasis with periportal infiltration by eosinophils (to be described in detail). By December 15 the pruritus had disappeared and on December 21 the serum bilirubin had fallen from a value on admission of 12.4 mg. per cent to 6.1 mg. per cent and the alkaline phosphatase, initially 36.4 King-Armstrong units, was 30.4 King-Armstrong units. Oral cholecystography showed normal filling of the gall bladder with no evidence of stones. The patient was discharged on December 28, 1955, at which time the serum bilirubin was 3.8 mg. per cent and she remained icteric for another week. The total duration of jaundice was about thirty days. On February 15, 1956, when seen in follow-up, she was asymptomatic. At that time, the serum bilirubin was 0.7 mg. per cent and the alkaline phosphatase 7.7 King-Armstrong units.

Case 3. This case demonstrates reaction to chlorpromazine with systemic symptoms, eosinophilia in the peripheral blood and intrahepatic obstruction *without* icterus.

H. M., a thirty-three year old divorced white woman, was admitted to the Psychiatric Service on November 4, 1955, because of an agitated depression. During a six-day period, beginning on October 22, 1955, she was treated with chlorpromazine, starting with a dose of 25 mg. three times daily, and increased each day by 25 mg. per dose. On November 2, 1955, two days prior to admission, fever, malaise and generalized myalgias developed for which she received an injection of penicillin. At the time of admission these complaints continued and in addition the patient noted severe anorexia and headache. Physical examination disclosed moderate lethargy and a temperature of 100.4°F. There was no icterus. There was tenderness in the right upper quadrant and epigastrium, and the liver edge was palpable 2 cm. below the right costal margin. The white blood count was 15,950 per cu. mm. and a differential count showed 8 per cent eosinophils. On November 8 epigastric tenderness was still present and the temperature had fallen to normal. On that date the serum bilirubin was 1.1 mg. per cent and the alkaline phosphatase, 20.9 King-Armstrong units. The serum total protein, albumin and globulin were normal and the cephalin flocculation test was negative. She remained asymptomatic and on November 18 the serum bilirubin was 0.4 mg. per cent and the alkaline phosphatase had fallen to 10.3 King-Armstrong units. The serum albumin and globulin were normal and the cephalin flocculation, negative. At no time was the patient clinically jaundiced, nor were dark urine or light stools ever seen. On December 9, 1955, an oral cholecystogram showed normal filling and emptying of the gall bladder with no evidence of stones. On March 19, 1956, she was discharged for further psychiatric care in another institution, and at that time she had no physical symptoms and physical examination was within the limits of normal.

Case 19. In the following case, leukopenia and a positive Rumpel-Leede sign developed in association with obstructive jaundice. The hematologic abnormality subsided without serious complication, but agranulocytosis with a fatal outcome has been reported [7].

E. B., a fifty-four year old white woman, was admitted to The Mount Sinai Hospital on January 24, 1956, with a three-week history of recurrent anterior chest pain, persistent for two days prior to admission. On physical examination, the patient was afebrile and no physical abnormality was found but the electrocardiogram revealed an acute diaphragmatic myocardial infarction. Because she was uncooperative and emotionally labile, a psychiatrist was consulted who described the patient as a narcissistic, demanding, suspicious person. He prescribed treatment with chlorpromazine which was started on January 31 with a dose of 300 mg. daily. On February 9 the patient became febrile and remained so for seven days. On February 13 a generalized maculopapular eruption appeared and the white blood count was 3,200 per cu. mm. Coincidentally, jaundice was first noted and the liver edge was felt 2 cm. below the right costal margin. Chlorpromazine administration was stopped on this day. On February 14 the serum bilirubin was 2.5 mg. per cent and the alkaline phosphatase was 34.7 King-Armstrong units. On February 16 a tourniquet test was positive but the white blood count had risen to 5,900 per cu. mm. The prothrombin time was normal. The white cell differential count revealed 3 per cent eosinophils. By February 24 the bilirubin had fallen to 1.3 mg. per cent and the alkaline phosphatase was 27 King-Armstrong units. The remainder of the hospital course was uneventful.

Case 18. In this case chlorpromazine was administered five months after an untoward reaction, probably including jaundice, to the same drug.

A. M., a fifty-three year old married white man, suffered from episodes of severe anxiety. In August,

1955, he was treated with chlorpromazine, 25 mg. twice daily, for two weeks. At the end of that period fever, malaise and myalgias developed. The fever lasted for four days but two days after its onset he noted very dark urine which persisted for one week. Weakness lasted for an additional two weeks and then he returned to work. The patient was not aware of jaundice during the episode but he was not observed by a physician at the time.

On January 27, 1956, because of recurrence of anxiety, chlorpromazine was again prescribed. He took one 10 mg. tablet on that day. During the same evening upper abdominal and mid-back pain developed. The following morning the pain had subsided but his urine was again dark. No fever or chills developed. He was admitted to The Mount Sinai Hospital on February 1 where he was found to be slightly icteric. The liver edge was felt one cm. below the right costal margin and was non-tender. The laboratory findings (Table I) were those of obstructive jaundice; the bilirubin then was 2.5 mg. per cent and there was a 4 per cent eosinophilia in the peripheral blood. The jaundice persisted for a total of two weeks and the patient was discharged on February 13, 1956, with a bilirubin of 0.93 mg. per cent. One month later he was well except for anxiety.

REVIEW OF LITERATURE

Reports of seventy-two cases of jaundice associated with chlorpromazine therapy appearing in the literature have been reviewed. Other instances were mentioned as having occurred but there was no further elaboration. From these seventy-two cases we have selected twenty-seven [*2*,6,7,8†,9,10,11‡,12–19*], which were sufficiently well documented and free of complicating factors to permit analysis at second hand with a reasonable degree of confidence. (Table II.) Notable among the contributions not included are the twenty cases of Kelsey et al. [*1*]. whose data were obtained by questionnaire and presented in tabular form. (Some of their findings will be discussed subsequently.)

Of these twenty-seven cases from the literature, the average age of the patients was fifty-one (thirty to seventy-eight) and 68 per cent were women. Sixty per cent had been given chlorpromazine in the treatment of psychiatric disorders; the others received the drug in the treatment of the pruritus of dermititis, Ménière's disease, duodenal ulcer and nausea. The average total dose received was 1,223 mg. over an average of 17.6 days. Prodromal systemic symptoms were noted in twenty-one, the prodrome lasting an average of 5.7 days (two to fourteen days), onset being on an average of 14.7 days (two to twenty-five days) after the start of chlorpromazine therapy. The prodrome was characterized by fever in at least 48 per cent and chills in 26.6 per cent. Nausea was prominent in 52 per cent, vomiting in 26 per cent and upper abdominal pain was notable in 30 per cent. An occasional patient complained of myalgias, loose stools or excessive weakness. Pruritus was moderate or marked in at least 70 per cent, either during the prodromal symptoms or later. Jaundice was noted on the average of twenty days (six to thirty days) after the first dose of chlorpromazine. The liver was palpable in at least 63 per cent, the liver edge usually was felt no more than 4 cm. below the right costal margin although in one case [*10*] it was felt 10 cm. down. Tenderness over the liver was noted in 33 per cent. The spleen was palpable in only one case [*10*]. All twenty-seven patients were frankly icteric. The alkaline phosphatase was elevated in all cases where recorded, the highest reported value being 119 King-Armstrong units [*17*]. The cephalin flocculation test (or the thymol turbidity test) was negative in twenty-one cases; in two cases (both from the same laboratory) the cephalin flocculation test was 2+ and in four it was 1+. The highest serum cholesterol recorded was 610 mg. per cent (lowest 190 mg. per cent), with an average value of 342 mg. per cent. The serum total protein was normal in all recorded cases. The prothrombin time was normal, when recorded, except in two cases. The percentage of eosinophils in the peripheral blood was recorded in nine cases: 2, 4, 7, 8, 16, 17, 17, 21 and 42 per cent.

Liver biopsy was performed in fourteen cases; the histologic findings will be discussed later. Seven patients were subjected to surgical exploration before the diagnosis of chlorpromazine jaundice was confirmed.

The jaundice persisted from seven to one hundred fifty-six days, an average of forty-three days.

DISCUSSION OF CLINICAL FEATURES

The clinical features of chlorpromazine jaundice seem from the foregoing to be quite uniform. The syndrome defined by the cases presented here and by those selected from the literature occurs about two weeks after the initial dose of chlorpromazine, bearing no relationship to the

* Cases 1 and 4.
† Case 1.
‡ Cases 1 and 2.

TABLE II

SUMMARY OF CLINICAL FEATURES

	Twenty-two Observed Cases	Twenty-seven Cases from the Literature
Average total dose	1,260 mg. (range 10–5,700)	1,223 mg. (range 38–2,850)
Average duration of therapy	15 days	17.6 days
Interval from first dose to onset of prodrome	14 days (range 6–42)	14.7 days (range 2–25)
Interval from first dose to onset of jaundice	18.6 days (range 11–29)	20 days (range 6–30)
Average duration of jaundice	30 days (range 7–122)	43 days (range 7–156)

	Incidence in Observed Cases		Incidence in Cases from the Literature	
	No.	%	No.	%
Prodromal symptoms	20	91	21	78
fever	15	68	13	48
chills	8	36	8	27
nausea	5	23	14	52
vomiting	5	23	7	26
abdominal pain	12	55	8	30
pruritus	13	59	19	70
Jaundice	20	91	27	100
Palpable liver	18	82	17	63
Tender liver	5	23	9	33
Palpable spleen	0	0	1	4
Elevated serum bilirubin	21	95	24 (of 24)	100
Elevated serum alkaline phosphatase	21	95	24 (of 24)	100
Positive cephalin flocculation test*	0	0	0	0
Hyperglobulinemia	0	0	2	7
Eosinophilia (in peripheral blood)	14 (of 17)	82	8 (of 9)	89
Exploratory laparotomy	1	5	7	26

* Above 2+.

daily or total dose taken; and, in our experience, no relationship to the presence of previous liver disease.

The disorder is usually initiated by an episode of systemic symptoms occurring about two weeks after the first dose of chlorpromazine. These prodromal symptoms commonly consist of fever, chills, pruritus, upper abdominal pain, nausea and myalgias. The systemic symptoms coincide with the onset of jaundice in one-third of the cases but otherwise are antecedent by about a week and persist for four or five days. Dark urine and light or clay-colored stools preceded the onset of jaundice by a few days. Typically, the patient is seen at the time of icterus, with pruritus his only complaint. The liver is usually enlarged, rubbery and, perhaps, slightly tender. A modest elevation of the erythrocyte sedimentation rate is common. Of much more help diagnostically is the eosinophilia found early in the peripheral blood in two-thirds of the cases. On occasion this may range as high as 26 per cent of the white blood cells.

The chemical characteristics appear to be uniformly "obstructive." There is an elevation of the serum bilirubin and alkaline phosphatase, the latter at times being out of proportion to the former and returning to normal more slowly (authors' Cases 11, 17, 19; Case 3 of Loftus et al. [*17*]). The serum cholesterol is also elevated,

reaching its peak sometime after the peak of bilirubinemia. Characteristically, the tests for parenchymal liver damage remain negative.

Although the jaundice may persist for as long as four months (Case 8), in our experience all patients have recovered uneventfully and without the development of cirrhosis over the period of observation. We have found no evidence that prolonged strict bed rest enhances the rate of recovery, compared to limited activity about the ward or home. However, this aspect of the study was not controlled sufficiently to permit a firm conclusion to be drawn.

Although the outcome of chlorpromazine jaundice was invariably benign in our series, six fatalities have been recorded [*2–4,7*]. Review of each of these reveals that in no case was death unequivocally attributable to chlorpromazine jaundice itself. One patient died of agranulocytosis due to chlorpromazine [*7*], another had rheumatic heart disease, mitral and aortic valvulitis, congestive failure and purulent pericarditis [*3*]. An editorial in the *British Medical Journal* describes another death, but in addition to (or instead of) chlorpromazine jaundice, the patient also had "cirrhosis and delirium tremens" [*4*]. One patient (Case 2) reported by Isaacs et al. [*2*] had, in addition, carcinoma of the breast, infectious hepatitis (ten weeks before death), and was receiving estrogen therapy. These authors also report a mortality [*2**] with common duct stone, abdominal surgery and gastrointestinal hemorrhage. The sixth death is reported by the same authors and was found by questionnaire. The patient was an eighty-one year old woman in a mental hospital in whom jaundice developed a month after she was started on chlorpromazine therapy and she died ten weeks later. No details of the case are given.

Only one of our patients received retreatment with chlorpromazine after a previous known untoward reaction which probably included jaundice. In this instance the jaundice recurred. In contrast to this experience, Elkes and Elkes [*20*] and Harper (cited by Winkelman [*21*]) have reinstituted chlorpromazine without recurrence of jaundice, while in Garmany's case [*22*] fever developed with each attempt to restart treatment.

The principle problem facing the clinician is not one of therapy but rather the differentiation of chlorpromazine jaundice from the causes of extrahepatic biliary obstruction. The frequency with which patients reported on in the literature have been explored surgically emphasizes the importance of making this critical distinction as well as the difficulty encountered in doing so. Indeed, seven patients were explored for possible common duct obstruction, representing 25 per cent of the literature included here. The history of chlorpromazine administration, and the clinical and laboratory features already discussed, in addition to normal x-ray studies of the duodenum and gall bladder or bile ducts, should lead to the correct decision in most cases. The additional evidence afforded by liver biopsy has proven, in our experience, often to be of great value.

* Case 3.

PATHOLOGIC FEATURES

In five of our cases liver biopsy was performed by means of the Vim-Silverman needle. A sixth patient was subjected to laparotomy and at the time of surgery a wedge biopsy specimen of the liver was obtained. The following are summaries of the histopathologic features in individual cases:

CASE 1. (Patient, A. G. Needle biopsy of the liver was performed forty days after the onset of jaundice, forty-three days after the last administration of chlorpromazine.) The lobular architecture was intact. There was a moderate increase in cellularity of the portal fields made up predominantly of lymphocytes but with some eosinophilic and neutrophilic leukocytes also present. Neither periportal fibrosis nor bile duct proliferation was found. Bile stasis was present, with many bile thrombi in often dilated bile capillaries and a heavy deposit of granular brown pigment was found within the central-lobular liver cells. Evidence of regeneration of parenchymal cells was prominent with many double and giant nuclei and occasional mitosis.

CASE 2. (Patient E. W. Needle biopsy of the liver performed thirteen days after the onset of jaundice, thirty days after the last administration of chlorpromazine.) The lobular architecture was intact. The portal fields showed only a moderate increase in cellularity and this consisted primarily of lymphocytes, although a few polymorphonuclear neutrophils and a smaller number of eosinophilic leukocytes were seen. There was no fibrosis or bile duct proliferation. The interlobular bile ducts were not dilated and were empty. Many bile thrombi were present within dilated bile capillaries throughout the lobule, but more prominent centrally, as was a brown granular pigment which stained the parenchymal cytoplasm. There was a moderate degree of parenchymal regeneration with giant nuclei and occasional mitosis.

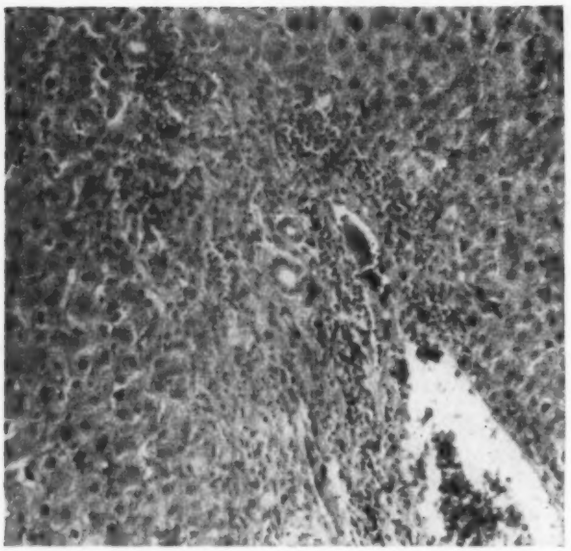

FIG. 1. Case 22. Portal field showing infiltration with inflammatory cells, many of which are eosinophils. Note the empty, undistended bile duct. Hematoxylin and eosin; original magnification, × 400.

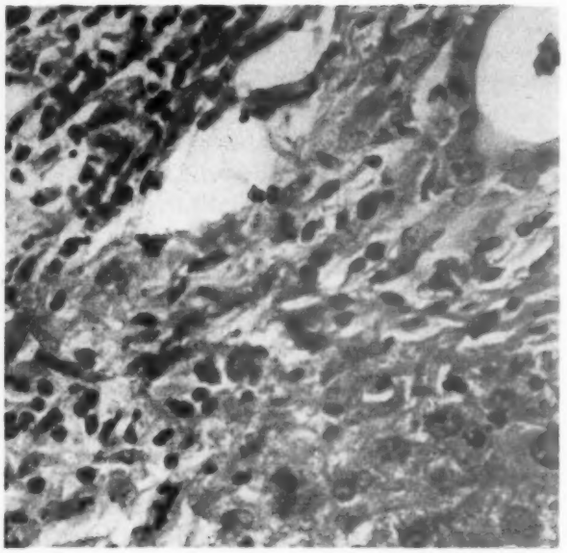

FIG. 2. Same case. Edge of a portal field showing infiltration by eosinophils and other leukocytes. The bile duct at upper right contains several clumped polymorphonuclear leukocytes. Hematoxylin and eosin; original magnification, × 620.

CASE 4. (Patient L. B. Needle biopsy performed five days after the onset of jaundice, two days after the last administration of chlorpromazine.) The lobular architecture was well preserved. There was good sampling of portal fields showing heavy infiltration by eosinophilic leukocytes and by many polymorphonuclear neutrophils, as well as a few lymphocytes. There was no evidence of fibrosis or bile duct proliferation. The bile ducts showed no distention and were empty of bile. In a few fields, white cells could be found within bile duct lumens and infiltrating bile duct walls. Bile stasis was evidenced by many bile thrombi within bile capillaries, many of which were dilated. These changes were most prominent around the central veins but could be identified out to the periphery of the lobules. Also more prominent in the central lobular areas were many parenchymal cells containing brown, coarsely granular pigment. A few parenchymal cells showed pyknotic nuclei and there were a moderate number of double nucleated and giant nucleated cells. Occasional mitotic figures were identified.

CASE 6. (Patient B. B. Needle biopsy performed six days after the onset of jaundice, twenty days after the last administration of chlorpromazine.) The lobular architecture was intact. The portal fields showed a heavy infiltration by eosinophilic leukocytes and a smaller number of polymorphonuclear neutrophils and lymphocytes. In scattered areas a few white cells were seen in the walls and within the lumens of interlobular bile ducts. The bile ducts were otherwise normal, empty of bile and not distended. In the central-lobular areas there was a moderate amount of granular brown pigmentation of the cytoplasm of many parenchymal cells, and a large number of bile thrombi within slightly dilated intercellular bile capillaries. The hepatic parenchyma appeared normal, except for frequent giant or double nuclei and a moderate number of mitotic figures.

CASE 7. (Patient R. G. Needle biopsy performed fifteen days after the onset of jaundice, twenty days after the last administration of chlorpromazine.) The lobular architecture was well preserved. The sampling of portal fields was inadequate but in those present there was a moderate degree of cellular infiltration consisting chiefly of lymphocytes with a few polymorphonuclear leukocytes and plasma cells; no eosinophils were seen. The bile ducts appeared normal in caliber and were empty of bile but in several instances contained a few white blood cells. There was no evidence of bile duct proliferation. Granular brown pigment was seen within parenchymal cells, as well as a moderate number of bile thrombi within the bile capillaries, most prominent in central-lobular areas but present out to the limiting plate. The hepatic parenchyma showed regenerative changes with many giant and double nuclei and a moderate number of mitoses. There was slight fatty infiltration. The regenerative changes were more prominent near the central veins but were present throughout the lobule.

CASE 22. (Patient S. G. Wedge biopsy at the time of exploratory laparotomy performed ten days after the onset of jaundice and on the day of the last

administration of chlorpromazine.) The lobular architecture was intact. There was a marked increase in cellularity within the portal fields, made up predominantly of eosinophilic leukocytes but with large numbers of neutrophils and some lymphocytes also present. In several areas white cells were found within the walls and clumped within the lumens of bile ducts. There was no periportal fibrosis or bile duct reduplication. The bile ducts were empty of bile and of normal caliber. Bile stasis was most prominent in the centrallobular areas with large numbers of bile thrombi within dilated bile capillaries. Evidence of regeneration of liver cells was prominent, with mitoses moderate in number. Near the central veins the liver cords were more widely separated than usual and the space of Disse was often clearly delineated. (Figs. 1 and 2.)

TABLE III
RELATIONSHIP OF PERIPORTAL EOSINOPHILS TO TIME OF BIOPSY AND PERIPHERAL BLOOD PICTURE IN SIX CASES OF CHLORPROMAZINE JAUNDICE

Degree of Periportal Infiltration by Eosinophils	Interval between Onset of Jaundice and Day of Biopsy (days)	Per cent of Eosinophils in Peripheral Blood at Time of Biopsy
Marked	5	6
Marked	6	20
Moderate	10*	..
Slight	40	7
Absent	15	3
Absent	13	1

* Patient still receiving chlorpromazine at the time of biopsy.

The histopathology was characterized in all cases by bile stasis and periportal inflammatory cell infiltration. Evidence of hepatic parenchymal regeneration was also present. The normal lobular architecture was invariably preserved. In three instances the periportal infiltrate was made up largely of eosinophils and in one additional case a significant number of eosinophils was present.

In those cases in which the time interval between the onset of jaundice and liver biopsy was short (less than one week) the eosinophilic component of the periportal infiltrate was most striking. (Table III.) In one instance (Case 22) in which predominantly eosinophilic infiltration was found ten days after the onset of jaundice, chlorpromazine was still being administered at the time of the biopsy. In the three remaining cases in which jaundice had been present for two weeks or more and chlorpromazine had not been administered more recently than three weeks prior to biopsy, the periportal cellularity was less prominent and was composed mainly of lymphocytes with few or no eosinophils present. Our cases are too few in number to permit a secure conclusion to be drawn from these observations; however, the implication of the trend is that eosinophils in the periportal infiltrate are an early finding, being most prominent during the first week of jaundice.

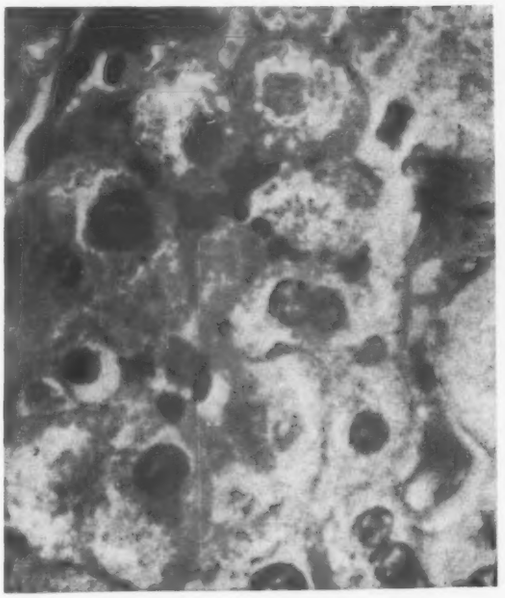

FIG. 3. Case 22. Area of an hepatic lobule near the central vein, showing inspissated bile within dilated intercellular bile capillaries. Hematoxylin and eosin, × 685.

The degree of eosinophilia in the peripheral blood correlated only roughly with the degree of periportal eosinophilic infiltration. Again the small number of cases involved makes it impossible to draw any firm conclusion.

Intracanalicular inspissation of bile was a prominent feature in all cases and tended to be more intense near the center of the lobule. The involved bile capillaries were often distended but adjacent liver cells were not abnormal and bile lake formation was absent. The finding of moderate evidence of liver cell regeneration in four of the six cases was unexpected in view of consistent failure of the clinical laboratory findings to demonstrate parenchymal damage. These regenerative changes are interpreted as a result of concomitant parenchymal cell loss even though direct histologic evidence of this is lacking. (Figs. 3 and 4.)

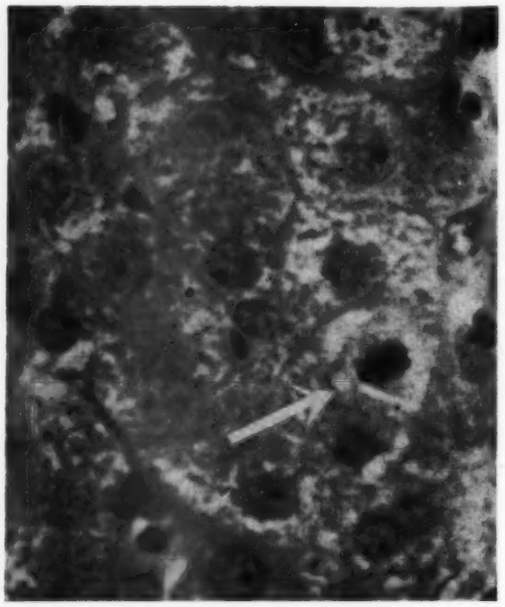

FIG. 4. Case 22. Section of liver showing a nucleus in mitosis. Hematoxylin and eosin, × 885.

In the three cases in which a heavy periportal infiltrate was present, white blood cells were found within the walls or lumens of the bile ducts, thereby satisfying the strict criteria for the histologic diagnosis of cholangitis [*23*]. In no case was periportal fibrosis, bile duct proliferation or interlobular bile duct distention found.

Liver biopsy findings have been reported in fourteen of the cases reported in the literature and included in this review [*6–13,15,17*]. In most instances the descriptions published are too brief to permit interpretation of the results with any degree of confidence. The following points are of interest. The presence of intracanalicular bile thrombi is reported in all cases. In seven cases there was inflammatory cell infiltrate within the portal fields [*6–8, 10–12*]; in two instances the presence of eosinophils was specifically noted [*10,12*]; however, Movitt et al. [*10*] refer to H. Popper's opinion (personal communication) that eosinophilic periportal infiltration is a significant diagnostic feature. In three cases specific mention was made of the absence of increased cellularity of the portal fields [*9,10*]. Two cases were reported to show parenchymal cellular damage [*10,12*]; one case each showed regenerative changes [*7*] and slight periportal fibrosis [*10*], respectively. An effort was made to relate a variety of clinical features such as interval between chlorpromazine administration, onset of jaundice and time of biopsy, or the presence of peripheral blood eosinophilia with the histopathology but no significant correlation could be found.

In a recent article Gambescia et al. [*30b*] report the presence of periportal infiltration by histiocytes and large numbers of eosinophils in at least four of eight liver biopsy specimens which were obtained during the course of chlorpromazine jaundice. However, in two cases in which sections of liver were obtained about one month after the onset of jaundice, Stein and Wright [*30c*] found no periportal inflammatory reaction.

It should be mentioned that in two cases reported by Isaacs et al. [*2*] "central lobular necrosis" and "diffuse hepatic necrosis" were noted. These cases were complicated by "infectious hepatitis" and by "common duct obstruction by stone . . . surgery and gastrointestinal bleeding," respectively, thereby making any relationship between chlorpromazine administration and the pathologic condition of the liver highly speculative. The clinical material presented in a series of twenty cases collected by questionnaire [*1*] has been excluded from previous discussion because of the lack of clinical details needed for purposes of our analysis. The pathologic descriptions are mentioned here because they are in part at variance with our findings. The summarized description of four of these cases is in agreement with our findings; however, one patient [*1**] showing acute diffuse hepatitis and two others [*1*†] showing cirrhosis are also reported. Again, the paucity of clinical information makes these difficult to evaluate, but these cases were clinically as well as pathologically atypical and it would seem likely that they represent forms of liver disease other than chlorpromazine jaundice, or chlorpromazine jaundice superimposed upon another hepatic disorder.

Although the findings on liver biopsy are often indistinguishable from those in extrahepatic obstruction, the histopathology of the liver may play a conclusive role in differential diagnosis. Periportal fibrosis, bile duct proliferation or bile infarct formation are late and inconstant findings in extrahepatic obstruction [*24–28*] and, although significant by their absence in chlorpromazine jaundice, are not thereby diagnostic. The finding of increased periportal cellularity predominantly consisting of eosinophilic leukocytes in the presence of evidences of bile stasis

* Case 17

† Cases 18 and 20.

and parenchymal regeneration we consider to be virtually diagnostic. As already indicated, it appears that the characteristic histopathology of chlorpromazine is more likely to be found when liver biopsy is performed early in the course.

PATHOGENESIS

Evidence that chlorpromazine jaundice is essentially obstructive in nature is afforded by the patient with acholic stools and intense pruritus, as well as by the findings of the clinical laboratory. The normal or empty common duct found at the time of exploratory laparotomy (Case 22) [*7,9,10,12,13,18*] place the level of the obstruction within the liver itself. In this regard, the demonstration by Menguy et al. [*29*] that chlorpromazine may cause an elevation of pressure within the bile duct of the cholecystectomized mongrel dog (apparently as a result of depressed duodenal motility) is probably not applicable to chlorpromazine jaundice in man. In only one of our patients was there previous cholecystectomy, and none gave a history of disease of the gall bladder. The demonstration of a common duct of normal caliber at the time of surgery and the absence of bile in the interlobular bile ducts on microscopic examination makes distal common duct obstruction improbable as a significant pathogenetic mechanism.

Whether the intrahepatic cholestasis demonstrated histologically is a result of an allergic reaction or a direct toxic effect in peculiarly predisposed individuals is, at present, problematic. The evidence available would seem to indicate that an allergic or at least idiosyncratic reaction is probably involved. Although none of our patients gave a clear-cut history of previous allergic reactions, the experience of other observers [*13,30a*] is that this may frequently be found. There are certain features apparent in this analysis of our own cases and in the experience recorded elsewhere which are often characteristic of the hypersensitive response as it is commonly recognized. Noteworthy among these features is the latent period, or delayed nature of the reaction to chlorpromazine, systemic prodromata usually developing more than a week after the start of therapy, and followed within a period of days by jaundice. Sussman and Sumner [*14*] have reported acceleration of this reaction during a second trial of therapy in a well documented case study. In their patient, who had recovered from chlorpromazine jaundice three months previously, a systemic reaction developed within several hours after a single small dose of chlorpromazine had been given and three days later the patient was found to have an elevated serum bilirubin. Gambescia et al. [*30b*] have reported a case in which an accelerated reaction to chlorpromazine occurred on two separate occasions when this drug was administered following recovery from an initial episode of chlorpromazine jaundice. We have had a similar experience (Case 18) in which an accelerated reaction was noted when chlorpromazine was given to an individual who had previously recovered from chlorpromazine jaundice. The frequent findings of eosinophilia in the peripheral blood of patients with chlorpromazine jaundice also favors the allergic theory, as does the local invasion of the connective tissue stroma of the portal areas by eosinophilic granulocytes. In addition, there is direct evidence that chlorpromazine is allergenic in a considerable number of individuals exposed. Contact dermatitis in nurses handling chlorpromazine preparations has been reported [*31*], and Lehman and Hanrahan [*32*] have found urticaria and asthma to occur in 13 per cent of patients receiving the drug. Finally, the lack of relationship between the occurrence of jaundice and the size of the dose administered favors an idiosyncratic or allergic response. It is difficult for us to explain the reports [*20–22,30a*] in which therapy was reinstituted after recovery from chlorpromazine jaundice without untoward effect. It is our impression and that of others [*7,9,10,16*] that the response to ACTH is disappointing. This is not necessarily damaging to the allergic theory if one considers that the prolonged icterus is a result of an acute injury which must undergo the natural processes of repair over a period of time.

The histologic picture described, empty interlobular bile ducts and inspissated bile present within the intercellular bile capillaries, would seem to place the site of obstruction between these two, that is, in the cholangioles, although no histologic alteration of the cholangioles could be found. Whether the obstruction is functional, caused by increased permeability of the cholangioles, or mechanical is uncertain. The inconstancy of the degree of periportal cellular infiltrate and its apparent resolution while the obstructive jaundice persists makes it unlikely that this is of pathogenetic significance Of interest in this regard is the absence of periportal infiltration noted in the reported cases of methyltestosterone jaundice (vide seq.) The occasional

paucity of bile thrombi would make it seem more likely that these are secondary to the cholestasis rather than of primary importance. We have been unable to find histologic evidence to support the point of view that swelling of liver cells, which thus compress bile capillaries, results in the central accumulation of bile pigment [*33*]. Our interpretation of the findings and our conclusions therefore are essentially those of Watson and Hoffbauer in their study of prolonged hepatitis with primarily obstructive features occurring in the course of (or as a form of) viral hepatitis [*34*]. To this variety of intrahepatic cholestasis these authors applied the term cholangiolitic hepatitis, implying thereby a functional disturbance of the cholangioles despite the absence of direct histologic evidence of cholangiolar damage. Popper [*35*] has demonstrated clear histologic evidence of cholangiolar injury in rats with ethionine hepatitis. He has also found similar changes in human hepatitis.

It would seem proper to consider as a group those cases of intrahepatic-obstructive jaundice which follow the administration of an apparently heterogeneous group of medications, of which chlorpromazine is one. In 1940 Hanger and Gutman [*35*] first separated this form of jaundice, in patients receiving arsphenamine, from other varieties of hepatitis and clearly defined the attendant clinical syndrome and pathologic features. They pointed out that a similar picture had been noted following use of toluylenediamine [*37*] and dinitrophenol. Since that time obstructive jaundice has been described following administration of thiouracil [*38*], methyltestosterone [*39–41*] and sulfadiazine [*42,43*]. A review of the cases reported by these authors reveals a striking similarity of clinical features with the experience in chlorpromazine jaundice, including the lack of relationship to the size of the dose, the reaction being apparently on the basis of idiosyncrasy or allergy. The "flu"-like prodromata, the relative freedom from important systemic symptoms during the height of the jaundice, the prominence of pruritus, the laboratory findings indicative of biliary tract obstruction, the eosinophilia and the uncertainty of response to further administration of the same medication all support this view. The descriptions of the histologic changes in the liver are also entirely compatible, although in methyltestosterone jaundice no periportal infiltrations have been described.

Despite the heterogeneous structure and pharmacologic actions of the drugs involved, the similarity of clinical and pathologic findings would indicate that a single mechanism is operating in all instances. It would seem reasonable to draw an analogy between this group and the obstructive form of prolonged viral hepatitis (viral cholangiolitic hepatitis) and to apply to it the term toxic-allergic cholangiolitic jaundice.

THERAPY

Among our own cases therapy varied considerably, but patients generally were kept in bed until jaundice had cleared or had reached a plateau, and then gradual mobilization was accomplished. Since anorexia was uncommon during the stage of jaundice, a high caloric diet was usually taken without difficulty and vitamin supplements were not regularly prescribed. In only one case (Case 15) was ACTH administered, and in that instance for a six-day period without apparent influence on the natural regression of the jaundice. The use of ACTH or cortisone has been reported by others [*9,10,16,30b*] with varying results. In Case 1 of Van Ommen and Brown's series [*9*], the serum bilirubin continued to rise for two weeks after starting ACTH therapy, and then fell gradually over a month. The patient of Hodges and La Zerte [*7*] became increasingly jaundiced despite ACTH but this case was further complicated by agranulocytosis with a fatal outcome. A more encouraging report [*30b*] describes prompt improvement in clinical status and laboratory findings of two patients following treatment with ACTH or cortisone. In one of these patients a prompt relapse was noted on two separate occasions when ACTH or cortisone therapy was discontinued after courses of twelve days and thirty days, respectively.

Johnson and Doenges [*44*] have demonstrated prompt improvement clinically and biochemically following administration of ACTH in two patients with viral cholangiolitic hepatitis. In neither of these instances did recurrence take place following cessation of therapy. These authors suggest that a prompt response to ACTH may be of value in differentiating cholangiolitic hepatitis from extrahepatic biliary tract obstruction.

The use of antihistaminics and sodium dehydrocholate has not been beneficial [*16,30b*].

SUMMARY

1. Twenty-two cases of chlorpromazine jaundice are reviewed. These follow a more uniform

pattern t. an some previous reports indicate and are consistent with the concept that chlorpromazine jaundice represents a distinct syndrome.

2. The clinical syndrome defined by these cases is characterized by a brief, prodromal episode of systemic symptoms followed by a more or less prolonged period of intrahepatic biliary tract obstruction. The prodromal symptoms commonly consist of fever, chills, pruritus, upper abdominal pain and nausea, usually occurring about two weeks after the first dose of chlorpromazine and persisting for four or five days. Jaundice may appear coincidentally but usually occurs one week after the onset of systemic symptoms. At the height of the icterus other systemic symptoms usually have disappeared and pruritus may be the only complaint. The results of the laboratory tests characteristically are those obtained in obstructive jaundice, whereas the tests for parenchymal liver damage usually remain negative. A mild or moderate eosinophilia was found in the peripheral blood in over 80 per cent of the twenty-two cases in this series.

3. In none of the cases presented was there evidence of antecedent liver disease. In all cases recovery was complete without evidence of residual liver damage.

4. Liver biopsy was performed in six cases, all of which showed bile stasis and periportal inflammatory cell infiltration. Eosinophils made up a large part of the periportal infiltrate in three cases. It seems likely that this finding is most common when liver biopsy is obtained early in the course.

5. It is postulated that chlorpromazine jaundice is part of an allergic reaction to the drug, causing functional or mechanical biliary obstruction of the cholangioles similar to that known to occur with certain other drugs.

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Enlargement of the Parotid Gland in Disease of the Liver*

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A CURIOUS non-inflammatory enlargement of the parotid glands, usually associated with evident malnutrition, has been noted in many parts of the world. It has also been described, chiefly in Europe, with obesity,[1] diabetes mellitus[2] and alcoholic cirrhosis.[3] However it is not a familiar physical sign in this country. This presentation is concerned with six patients with liver disease in whom parotid enlargement was an impressive clinical finding. Specific disease of the glands was excluded by biopsy in four and is unlikely on clinical grounds in the others.

CASE REPORTS

CASE I. G. O., a forty-six year old white florist, was hospitalized at the Veterans Administration Hospital in Syracuse in 1955 for nervousness, anorexia and morning vomiting. At the age of seventeen he began to drink beer. By the age of twenty-five he had added 15 to 20 shots of whiskey daily and this was increased to more than a quart of whiskey daily at the age of thirty-seven. Food intake for many years was black coffee and pastry for breakfast; a sandwich, a quart of milk and an occasional bowl of soup for lunch; and either no evening meal or a little meat or green vegetable. He had severe jaundice at the age of ten with apparent complete recovery. Hypertension was known for two years.

The patient was an obese man with marked livedo reticularis of arms, chest and abdomen. The blood pressure was 165/105. The lacrimal glands were prominent. The parotid glands, visibly enlarged bilaterally, were smooth and non-tender to palpation. The orifices of Stensen's ducts were normal. The submaxillary glands were not enlarged. The liver, palpable 8 cm. below the right costal margin, was smooth, firm and non-tender. The testes were normal. There was moderate coarse tremor of the hands. There were no spider angiomas, no gynecomastia, and no skin or mucosal changes suggestive of vitamin deficiency.

The two-hour postprandial blood sugar was 193 mg. per cent. Bromsulphalein retention was 12 per cent in forty-five minutes. Prothrombin time was 85 per cent of normal. The total protein was 8.0 gm. per cent with 4.7 gm. of albumin and 3.3 gm. of globulin. The icterus index, cephalin flocculation test, serum alkaline phosphatase and serum amylase were normal.

A biopsy specimen of the liver was strongly suggestive of portal cirrhosis. Biopsy of the left parotid gland revealed slight fat infiltration.

CASE II. L. T., a thirty-two year old Indian housewife, was admitted to the Veterans Administration Hospital in Syracuse in 1955 for jaundice and abdominal swelling. Her urine was dark and her stools were light in color, with occasional melena. Three years earlier she had tuberculous pleural effusion and peripheral neuropathy. A biopsy of the liver at that time revealed marked fatty infiltration. The patient had been drinking alcohol heavily since the age of nineteen. For the past five years she had eaten irregularly and in the five months prior to admission she ate no more than two meals a week.

Examination revealed an obese, dark skinned, icteric woman with several spider angiomas of the chest. The blood pressure was 140/85. Symmetric non-tender parotid gland enlargement was obvious. The orifices of Stensen's ducts were normal. The lacrimal and submaxillary glands were not enlarged. The liver was palpable 6 cm. below the right costal margin and was smooth and non-tender. A fluid wave was elicited. Pretibial edema was marked. Neurologic examination was normal.

Glucose tolerance test showed a diabetic-type curve with 237 mg. per cent blood glucose at two hours. The cephalin flocculation test was 2+ in forty-eight hours. Thymol turbidity was 9.6 units. Serum bilirubin was 6.3 mg. per cent. Bromsulphalein retention was 28 per cent in forty-five minutes. Serum alkaline phosphatase was 6.8 Bodansky units. Prothrombin time was 50 per cent of normal. The serum total protein was 6.7 gm. per cent with 3.1 gm. of albumin and 3.6 gm. of globulin. The serum amylase was normal. Sputum studies for tubercle bacilli were negative and the x-ray of the chest was normal.

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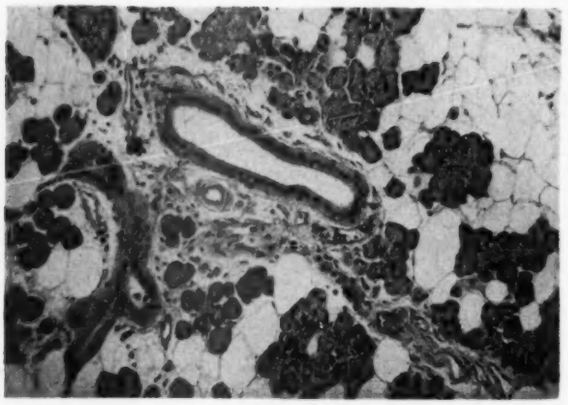

FIG. 1. Case II. Photomicrograph of biopsy specimen of the right parotid gland showing marked fat infiltration.

A biopsy of the liver showed portal cirrhosis. Biopsy of the right parotid gland revealed marked fat infiltration (Fig. 1).

CASE III. D. B., a fifty-two year old white housewife, was admitted to the Syracuse University Hospital in 1955 for hepatomegaly and a thyroid nodule found on routine physical examination. She had an illness with jaundice at the age of seventeen with no known sequellae. Excessive sweating, preference for cold weather and nervousness were always present. She drank at least two or three highballs daily. She claimed to eat regularly. Breakfast included toast, black coffee and an occasional egg; for lunch she had vegetable soup or a salad or a meat sandwich; supper included meat, a vegetable and sometimes potato.

She was obese, with plethoric facies and fine telangiectases over both cheeks, but no spider angiomas. Scleral icterus was present. The blood pressure was 166/90. Both parotid glands were markedly enlarged but non-tender. The orifices of Stensen's ducts were normal. The lacrimal and submaxillary glands were not enlarged. A small nodule was palpable in the left lobe of the thyroid gland. A prominent abdominal venous pattern was found. Shifting dullness was noted but a fluid wave was not elicited. The liver was palpable almost to the level of the right iliac crest and was firm, irregular and non-tender. The spleen was palpable 4 cm. below the left costal margin. Neurologic examination was normal. The skin, hair and eyes were not suggestive of hyperthyroidism.

Fasting blood sugar was 88 mg. per cent. The thymol turbidity was 33 units. The bromsulphalein retention was 6 per cent in forty-five minutes. Serum proteins, serum amylase, prothrombin time and cephalin flocculation test were normal. Radioactive iodine uptake by the thyroid gland was 30 per cent in six hours and 51 per cent in twenty-four hours.

A biopsy of the liver revealed "marked fatty cirrhosis."

CASE IV. R. O., a fifty-eight year old white laborer, was admitted to the Syracuse University Hospital in 1955 for pain related to an old fracture of his hip. He denied drinking more than an occasional glass of beer. Breakfast consisted of coffee, rolls and orange juice. For both lunch and supper he had a meat sandwich, a soft drink and a bowl of soup. Diabetes mellitus was diagnosed about ten months before admission but he did not follow a diet or take insulin.

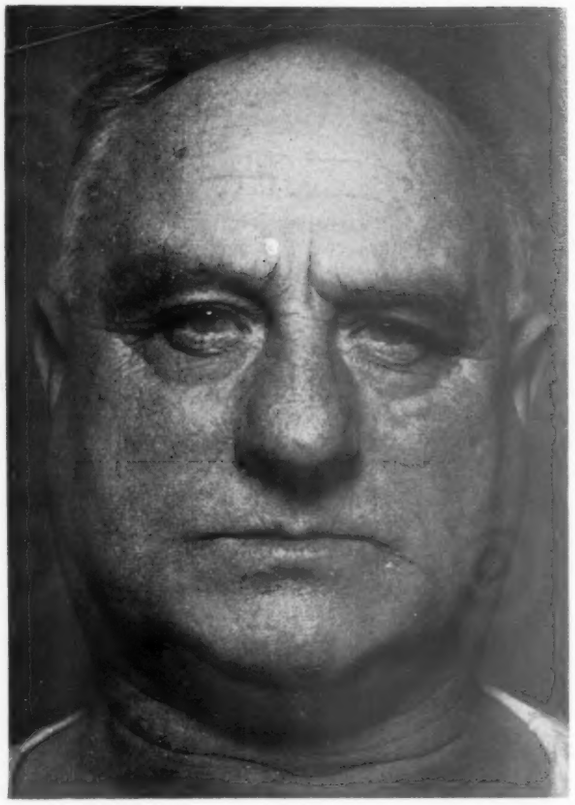

FIG. 2. Case IV. Frontal view showing symmetric parotid gland enlargement.

The patient was an obese man with a blood pressure of 170/110. Both parotid glands were enlarged but non-tender. (Fig. 2.) The orifices of Stensen's ducts were normal. The lacrimal and submaxillary glands were not enlarged. The liver was palpable 8 cm. below the right costal margin and was smooth and non-tender. Edema of the ankles was present. Motion of his left hip was limited. Neurologic examination was normal except for disorientation for time and extremely poor memory, which made the dietary history of doubtful validity.

On admission his blood sugar was 240 mg. per cent and a subsequent fasting specimen was 151 mg. per cent. Bromsulphalein retention was 16 per cent in forty-five minutes. Prothrombin time was 85 per cent of normal. The serum total protein was 6.1 gm. per cent with 4.2 gm. of albumin and 1.9 gm. of globulin. The cephalin flocculation test, serum alkaline phosphatase and serum amylase were normal.

A biopsy of the liver revealed fatty metamorphosis

and slight chronic pericholangiolitis. Biopsy of the right parotid gland showed moderate fatty infiltration.

CASE V. A. H., a forty-eight year old white steel worker known to have portal cirrhosis, was seen in the follow-up clinic of the Veterans Administration Hospital in Syracuse in 1955. At that time he was found to have bilaterally enlarged, non-tender parotid glands without enlargement of other salivary glands. This had developed in the five weeks following his discharge from the hospital. During that time the patient had eaten enormous meals and completely stopped his long-standing daily consumption of whiskey.

The recent hospitalization was for dyspnea, ascites and anasarca which were attributed to cirrhosis of the liver and pulmonary emphysema with cor pulmonale. At that time his parotids were not enlarged. He was an obese man with spider angiomas of the face and shoulders and livedo reticularis. The blood pressure was 130/70. He had a prominent abdominal venous pattern and ascites. The liver was palpable 7 cm. below the right costal margin. During the course of his hospitalization he had a short period of "flapping tremor" of the hands while on a high protein diet.

The fasting blood sugar was 84 mg. per cent. The cephalin flocculation test was 3+ in forty-eight hours. Bromsulphalein retention was 14 per cent in forty-five minutes. Prothrombin time was 63 per cent of normal. The serum total protein was 7.5 gm. per cent with 4.5 gm. of albumin and 3.0 gm. of globulin. Serum bilirubin was 1.5 mg. per cent. The thymol turbidity and alkaline phosphatase were normal. No biopsy of the liver or parotid gland was obtained.

CASE VI. I. C., a forty-nine year old housewife, was admitted to the Syracuse University Hospital in 1955 because of a bleeding gastric ulcer. Several years previously the patient had been told she was hypertensive and was given a low calorie diet for her obesity. Her weight was reduced from 220 to 185 pounds. She had begun drinking at the age of twenty-one. For the past fifteen years she had been drinking about 3 quarts of beer daily and a pint of whiskey or more each week. Her intake of food could not be accurately assessed.

Examination revealed an obese, tremulous woman. The blood pressure was 160/105, temperature 100.3°F., pulse 105, respirations 16. The skin was pale, without spider telangiectases. The retinal arterioles were narrowed and tortuous. The parotid glands were enlarged, especially the left. Stensen's ducts were normal. The submaxillary glands were not enlarged. The lacrimal glands were prominent. The liver was palpable 8 cm. below the right costal margin but was not tender. The spleen was not felt. Pretibial edema was present. The neurologic examination was negative except for the tremulousness.

The bromsulphalein retention was 24 per cent in forty-five minutes. Serum protein determinations showed 3.0 gm. per cent of albumin and 1.7 gm. per cent of globulin. Normal laboratory findings included: fasting and postprandial blood sugar, serum bilirubin, serum amylase, alkaline phosphatase, cholesterol and cholesterol esters, cephalin flocculation test and thymol turbidity.

A biopsy of the liver revealed fatty infiltration. Biopsy of the left parotid gland revealed slight to moderate fatty infiltration.

HISTORICAL REVIEW

Parotid Enlargement Associated with Evident Dietary Deficiency. In 1905 Sandwith[4] described painless bilateral parotid enlargement in Egyptian laborers with pellagra, the enlargement receding as the tongue regained its papillae. A few years later Fontoynont[5] and then Léri[6] made the same observation in non-pellagrins in Madagascar and Algeria; in Madagascar the deficient diet was characterized by an excess of white potatoes. During World War I parotid enlargement was noted in Polish children during a period of famine, disappearing as better food became available.[7]

In 1925 Miller[8] confirmed Sandwith's findings in Egyptian pellagrins and almost a decade later, Biggam[9] related parotid enlargement to ancylostomiasis in that country. Kenawy,[10] in 1937, defined more closely the nature of the parotid enlargement in Egyptians. He found about 2 per cent of the poorer farm workers so afflicted, males ten times as frequently as females. Of one hundred subjects with parotid enlargement, sixty-five had pellagra, thirty-one had cirrhosis (including twenty-five with pellagra), ten had diabetes mellitus and two had beri beri. Although most were obviously malnourished, a few were not. Histologic study of the enlarged glands showed an increase in the number of ducts, while the acini appeared to be unusually compact. Dietary supplements of protein and vitamins B_1, B_2, C and D did not decrease parotid size. X-ray therapy caused regression in nine of ten cases.

More recently, enlarged parotids have been found among severely malnourished South African Bantu tribesmen,[11] Malayan aborigines,[12] certain Negroes in Brazil[13] and the Muruts of North Borneo.[14] In France, Gounelle[15] related parotid enlargement to a variety of cachectic states.

The presence of parotid enlargement in a malnourished North American population was reported in 1955 by Sanstead, Koehn and Ses-

soms.[16] They found this condition in 3.5 per cent of 1,094 mental patients at St. Elizabeth's Hospital in Washington, D. C., and in 12 per cent of 165 American Indians in hospitals in the Southwest. This survey was reported together with a larger study of poorly nourished Asians in whom parotid swelling was related to caloric restriction, tenderness in the calves, pellagroid pigmentation, cheilosis and hypoproteinemia. However a specific etiologic factor could not be defined. Of interest in the American survey was the high incidence of males and of non-Caucasians in the affected group, and the inclusion of several patients with diabetes mellitus.

Parotid Enlargement during Recovery from Malnutrition. Several observers described parotid gland swelling in German soldiers returned from Russian prison camps following World War II,[17–20] and a similar finding was noted in Japanese soldiers on their repatriation from Russia.[21] In both groups parotid enlargement was so common that an epidemic disease was suggested. This swelling often developed after two or three weeks of large intake of food, was often accompanied by obesity, and disappeared slowly. In South Africa Davies[22] found that the first sign of improvement in kwashiorkor was enlargement of the parotids, the enlargement subsiding as improvement continued.

A single report by Hoelzel[23] on his personal experience with parotid enlargement is notable as a prototype of the refeeding variety of this syndrome. It first began when he ate freely of potatoes, bread and sauerkraut following a six-month restriction of calories and protein. He then limited himself to oranges and lemons for seventeen days and the parotid size decreased markedly. However liberalizing his diet to contain "plenty of vegetables like turnips" caused them to enlarge again. Bananas were then made the mainstay of his diet and the enlargement subsided. Thereafter, the size of the parotids increased when he was not on a "fruitarian" diet and decreased when he fasted or ate only fruit. Eventually, the enlargement became irreversible.

Parotid Enlargement in Obesity, Diabetes Mellitus and Portal Cirrhosis. In 1912 Sprinzels[1] reported enlargement of the parotids in thirty-three obese outpatients in a Vienna clinic. Nutritional histories are not available. Gynecomastia was present in seven case. Four patients had fasting glycosuria and in six of nine others glycosuria developed after 100 gm. of glucose by mouth. Examination of one enlarged gland revealed a normal microscopic picture.

In 1932 Flaum[2] reported symmetric enlargement of the parotids as a manifestation of diabetes mellitus. Sixteen of his twenty-seven patients had glycosuria and the others had impaired glucose tolerance. In general they belonged to a group characterized by sthenic habitus with a tendency to obesity and arterial hypertension and to enlargement and hardening of the liver. The incidence of specific liver disease or of alcoholism in these patients is not known. John[24] in this country described four obese diabetic patients with parotid enlargement whom he considered to have Mikulicz's syndrome, although none had lacrimal gland involvement.

Bonnin, Moretti and Geyer[3] reported from France in 1954 that a large number of their patients with fatty livers or with portal cirrhosis had large parotids.

TABLE I
DESCRIPTION OF PATIENTS IN PRESENT SERIES

Case	Age	Sex	Height (inches)	Weight (pounds)	Blood Pressure	Liver Disease	Impaired Glucose Tolerance
I	46	M	67	200	165/105	Portal cirrhosis	Yes
II	32	F	61	153	140/85	Portal cirrhosis	Yes
III	52	F	63	159	166/90	Portal cirrhosis	No†
IV	58	M	64	196	170/110	Fatty liver	Yes
V	48	M	65	182	130/70	Portal cirrhosis*	No†
VI	49	F	64	185	160/105	Fatty liver	No

* Clinical diagnosis; biopsy of the liver not obtained.
† Fasting blood sugar normal; glucose tolerance test not done.

COMMENTS

The cases reported here have three characteristics in common: parotid enlargement, obesity and liver disease. (Table I.) Enlargement of the submaxillary salivary glands was not present. Obesity was definite in all, but not of remarkable degree in any. The question comes to mind, whether or not the parotid swelling in these patients is simply one of the variations in fat distribution in obese people. However in our experience obese patients without liver disease do not have enlarged parotids. The severity of the liver disease ranged from hepatomegaly with mild impairment of bromsulphalein excre-

tion and fatty metamorphosis on histologic examination (Case IV) to frank portal cirrhosis with jaundice, ascites and spider angiomas (Case II). Biopsies of the liver in five patients revealed portal cirrhosis in three and fatty infiltration in two. Four of the patients drank alcohol heavily and one moderately. In one patient (Case V) parotid enlargement was noted three months after he had abstained from alcohol and had begun to eat extremely large amounts of food.

TABLE II
INCIDENCE OF DIABETES, OBESITY AND LIVER DISEASE IN CERTAIN EUROPEAN AND AMERICAN REPORTS OF PAROTID ENLARGEMENT

Author	Parotid Enlargement	Liver Disease	Diabetes	Obesity
Sprinzels, 1912	+	..	+	+
Flaum, 1932	+	+	+	+
John, 1933	+	..	+	+
Bonnin, 1954	+	+	..	..
Present Series	+	+	+	+

None of these patients showed signs of vitamin deficiency, nor did careful dietary histories suggest a specific deficiency pattern. One patient had clinical diabetes mellitus and two of the others had marked impairment of glucose tolerance, but the role of the hepatic disease in this impairment was not assessed. Three of six patients had definite diastolic hypertension, which is unusual in portal cirrhosis.[25] Two patients had pronounced livedo reticularis, involving both the trunk and the extremities.

All of these situations in which non-inflammatory enlargement of the parotids has been found may be grouped under the heading of nutritional disturbance. Caloric undernutrition as well as specific deficiency disease was present in the non-Caucasian populations with parotid swelling. However these findings were absent in the European and American series that relate most closely to our patients. Table II illustrates the similarity of these series, especially that of Flaum,[2] to the present one. Although liver disease and impaired glucose tolerance are not constant findings in association with parotid enlargement, they do occur in a considerable number of cases. Obese patients were excluded from the report of Bonnin.[3]

In Europe several investigators postulated a work hypertrophy of the parotids as a response to excessive caloric intake, particularly in the form of carbohydrates. Indeed, Bonnin[3] reported that his cirrhotic subjects showed histologic evidence of hypersecretion, and a high rate of amylase production in the parotid secretion. Against this concept, however, stand the occurrence of parotid enlargement in calorically undernourished populations and the absence of parotid enlargement in most obese patients. The single histologic specimen of parotid presented by Sprinzels,[1] and the four reported here, showed no evidence suggesting glandular hypersecretion.

Parotid enlargement may accompany many patterns of disturbed nutrition regardless of caloric intake, the state of glucose metabolism, or the presence of specific deficiency diseases. It seems to have the same significance as the hepatic disease which often accompanies it, pointing to disturbed nutrition but not defining the disturbance. However the patients described here fit into a syndrome characterized by parotid enlargement, liver disease, moderate obesity and a tendency toward arterial hypertension and impaired glucose tolerance. The obesity and the tendency toward hypertension are the clinical features which distinguish them from the larger number of patients with liver disease who do not have enlarged parotids.

SUMMARY

1. Six cases of non-inflammatory enlargement of the parotid glands in association with liver disease are described. Moderate obesity was present in all cases, arterial hypertension in three, and impaired glucose tolerance in three.

2. Similar parotid enlargement has been observed throughout the world in association with evident malnutrition or during recovery from starvation. In Europe and America it has appeared in clinical settings of liver disease, obesity, diabetes mellitus or combinations of these states.

3. This sort of parotid enlargement seems to have much the same significance as a fatty liver, pointing to disturbed nutrition or metabolism but not defining the disturbance.

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Blood Carotene in Steatorrhea and the Malabsorptive Syndromes*

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MALNUTRITION caused by defects of absorption is not rare; however the difficulty often is unrecognized in its earlier stages. The malabsorptive syndromes include certain types of hepatic and pancreatic disease, postgastrectomy disorders, insufficient small intestine (after resection or fistula formation), celiac disease and sprue, advanced regional enteritis and enterocolitis, amyloidosis and scleroderma of the intestine, intestinal tuberculosis, lymphosarcoma and intestinal lipodystrophy (Whipple's disease). There may be other entities associated with malabsorption but this classification of Cross and associates [*1*] is logical and convenient.

Improved screening tests and diagnostic methods are needed for earlier recognition of these disorders. The present study was undertaken to evaluate a procedure depending upon lowering of the blood level of carotene, or provitamin A, measured by a simple colorimetric determination, as a screening test for the malabsorption of fat. The results of this determination were compared with other available methods: quantitative excretion of fat in the feces, fat balance, x-rays of the gastrointestinal tract, duodenal intubation and pancreatic function studies, measurement of blood calcium and phosphorus, serum proteins and prothrombin time. Oral and intravenous glucose tests were performed when indicated. In some patients special studies were made with I-131 labeled triolein [*2*].

Unlike vitamin A, which is rapidly absorbed, carotene is a slowly absorbed fat-soluble material present normally in the diet. It is found chiefly in liver, kidney and certain colored vegetables and fruits, especially lettuce, carrots, spinach, tomatoes and apricots [*3*]. Since carotene is fat-soluble, the presence of lipid in the diet aids its absorption. On a fat-free diet 10 per cent of the carotene in the diet is absorbed [*4*]; when vegetable oil is administered, 40 to 70 per cent of the carotene may be absorbed [*5,6*]. On the other hand, administration of carotene in mineral oil or ingestion of mineral oil with meals prevents proper absorption of carotene, presumably by the increased solubility and retention of carotene in the non-absorbable oil in the bowel [*7*].

The principal source of carotenoid pigments in blood plasma is the diet. Although the liver of animals and humans contains carotene, the total body stores of this material must be quite limited, as suggested by the ease with which elevation and depression of the blood carotene level may be manipulated by dietary means. Several studies have demonstrated a marked rise in blood carotene when large doses of carotene in oil are administered to man [*8–11*]. When a single large dose is given this rise is slight in three to four hours, more evident in six to ten hours, and definite in twenty-four to forty-eight hours. The increase also is demonstrable when grated carrots are given in large quantities [*10,12*]. Administration of emulsifying agents such as bile salts or lecithin is reported to increase the rate of absorption in normal individuals but not in patients with cirrhosis of the liver [*9*]. In addition to the elevated carotene levels observed in carotenemia due to an excess intake of carotene, high plasma carotene levels also have been noted in hypothyroidism, diabetes and hyperlipemia. High fever [*13*], steatorrhea, liver disease and poor diet are the chief causes of low plasma carotene levels in man. Vitamin A and carotene depletion studies in man have clearly demonstrated the paucity of carotene stores in the body. Normal individuals receiving a diet low in carotene and vitamin A consistently demonstrated low levels of blood carotene within one week,

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concomitant with a fall in fecal carotene to 1 per cent of its original concentration [*14,15*]; the blood vitamin A levels were unaffected up to six months or longer [*15,16*]. In addition, both in animals [*17*] and man [*18*], the lowest levels of blood carotene were obtained during the winter

TABLE I
NORMAL RANGE OF PLASMA CAROTENE

Investigator	Range (μg./100 ml.)	Mean (μg./100 ml.)
Kimble [*22*]	50–300 (males)	166
	90–340 (females)	186
Harris [*19*]	90–340 (males)	210
	80–400 (females)	180
Kirk [*23*]	40–540	200
Murrill [*11*]	100–350 (males)	199
	140–420 (females)	277
Highman [*20*]	110–400 (males)	111
	130–400 (females)	244
Yudkin [*18*]	50–240	123
Yarbrough [*21*]	100–330	183
Caveness [*24*]	100–250	138
Popper [*25*]	42–150	81
Haworth [*26*]	49–344 (females)	121
Present series	70–282	123

months of December through March when fresh vegetables are more difficult to obtain, as compared with the highest levels during the fall months. The relationship of blood carotene to dietary intake thus is well established; low blood carotene levels have been reported in endemic malnutrition [*19–21*].

In normal individuals the blood carotene is fairly constant within a given range. Although methods for determination of plasma or serum carotene are quite variable, a similar pattern of normal range is clearly discernible. Using only those methods which refer to a standard of crystalline carotene, normal ranges are listed in Table I. The reports of May [*27*], Clausen [*28*] and Robinson [*29*] are omitted because they principally concern children. Some variation exists between males and females but for the study of carotene depletion this difference was ignored. In addition the reports of Kimble [*22*], Kirk [*23*], Yudkin [*18*], Popper [*25*] and Haworth [*26*] indicate that their lower limits of normal of 40, 42, 49 and 50 μg. per 100 ml. represent no more than a very few individuals. Hence for the purposes of this study they were assumed to be below the lower limit of the normal range; the reasons will become apparent later.

METHOD

In the forenoon 10 to 15 ml. of venous blood were drawn, preferably into oxalated bottles, but clotted blood was employed in a few instances. There was no significant difference between serum and plasma carotene in duplicate determinations. The method of Kimble [*22*] for plasma carotene was employed with a slight modification as recommended by Yudkin [*18*]. An equal volume of 95 per cent alcohol was added dropwise to 3 to 5 ml. of plasma with careful mixing to insure adequate release of carotenoid pigments from their bond to albumin. Petroleum ether then was used to extract the fat-soluble pigments. The light transmission was determined with a Junior Coleman spectrophotometer set at 440. The results are expressed in micrograms per 100 ml. Standardization with crystalline carotene (80 per cent beta and 20 per cent alpha) resulted in a curve almost identical with that reported by Kimble.

Fecal fat excretion was measured in hospitalized patients whose dietary fat intake was estimated from standard tables. The ordinary hospital diet contains 100 to 120 gm. of fat but patients with steatorrhea usually were given a 50 to 75 gm. fat intake. Fecal fat was measured in pooled three-day collections of feces by the method of Van de Kamer [*30*], using an aliquot of wet stool. A recent evaluation of this method by Woodman and Yeoman [*31*] yields results quite comparable to ours, that is, a normal mean of 3.91 ± 2.45 gm. of fatty acids per twenty-four hours, or an upper limit of normal of 5.0 gm. fatty acid. Because of the great variability of fat intake, the coefficient of absorption was calculated by the following formula:

$$\text{C.A.} = \frac{\text{Fat Intake (gm.) less Fatty Acids in 24 hr. stool (gm.)} \times 100}{\text{Fat Intake (gm.)}}$$

In normal persons the coefficient always exceeded 95 per cent; it has proved to be a more reliable index than the fecal fat output alone.

RESULTS

The distribution of plasma carotene in 110 individuals without organic gastrointestinal disease is shown in Figure 1. Most of these were patients under investigation for varied symptoms, usually gastrointestinal. The absence of organic disease was established by the usual diagnostic procedures. Of this group thirty-two patients were in the hospital and in them fecal fat studies were obtained. The mean plasma carotene level in the normal group was 123 μg. per 100 ml. with a standard deviation of 47. Because most normal individuals had levels of 70 μg. per 100 ml. and above, this was chosen as

the lower limit of normal. Six patients with normal fecal fat output had plasma carotene levels below 70 μg. per 100 ml. Each had been on a restricted diet prior to the test; indeed, the two patients with the lowest plasma carotene values (35 and 40 μg.) were eating almost no food, one

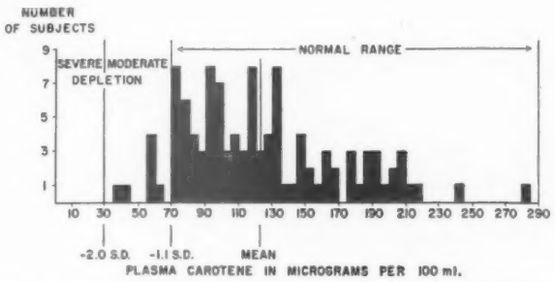

FIG. 1. Plasma carotene in absence of gastrointestinal disease (110 subjects).

in an attempt to lose weight vigorously, and the other during a borderline psychotic state.

The relation of plasma carotene to the coefficient of fat absorption was studied in thirty-two of the one hundred and ten individuals. (Table II.) Twenty-six of this group had normal coefficients of fat absorption and normal carotene levels; six were below the arbitrary normal limit of 1.1 standard deviations from the mean but none were below 2.0 standard deviations, which we considered evidence of severe depletion.

The relation of plasma carotene to the coefficient of fat absorption was investigated in thirty patients with malabsorptive diseases (Table II); fifty-eight determinations were made within one week of one another. Although the scatter is great, a linear relationship is suggested when the coefficient of absorption is plotted against the logarithm of the plasma carotene. (Fig. 2.) To confirm this the linear correlation coefficient (r), calculated in the ninety duplicate determinations, was found to be +0.45, highly significant at the 1 per cent probability level [*32*]. Seven patients with definite steatorrhea had normal plasma carotene levels. Two had involvement of only a small area of the small intestine with regional enteritis. Three had mild steatorrhea

TABLE II

RELATION OF PLASMA CAROTENE TO COEFFICIENT OF FAT ABSORPTION IN NINETY DUPLICATE STUDIES

Subjects	No. of Studies	Coefficient Absorption	Plasma Carotene (μg./100 ml.)				
Normal.....	32	95–100	0	2	4	15	11
Abnormal (30 patients)	8	90–94	2	3	2	1	..
	28	70–89	7	8	8	5	..
	13	50–69	8	4	1	..	..
	6	30–49	4	1	..	1	..
	3	10–29	2	1	..	..	..
			29	50	70	123	250
			Depletion			Normal	

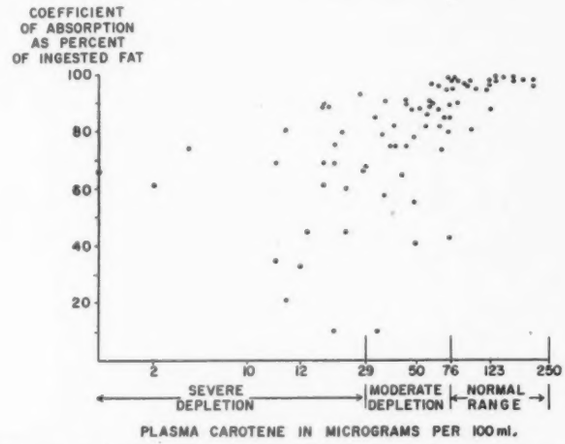

FIG. 2. Relation of plasma carotene to the coefficient of fat absorption.

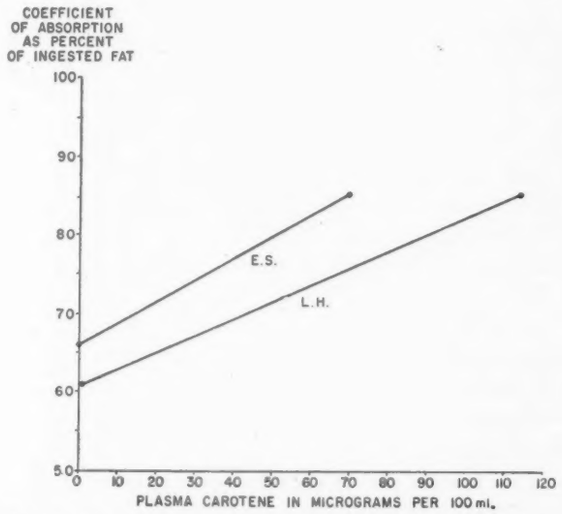

FIG. 3. Simultaneous improvement in plasma carotene and coefficient of fat absorption during prednisone therapy in sprue.

secondary to the postgastrectomy syndrome; one had non-tropical sprue and was receiving steroids; and one had hepatitis in an early phase of the disease. In the remaining fifty-one determinations steatorrhea and a low plasma carotene were both present; some carotene levels were lowered only moderately, but in a few patients with sprue only minute quantities of carotenoid pigment were found in the blood plasma.

TABLE III

IMPROVEMENT IN PATIENTS WITH NON-TROPICAL SPRUE DURING STEROID THERAPY

Patient	Age and Sex	Date	Carotene (μg./100 ml.)	Coefficient of Absorption (per cent)	Steroid Dose (mg./day)	Clinical Response
M. Q.	46, F	5/25/55	8.9	69	.....	.....
		6/29/55	36.	..	100 mg. cortisone	Fair
		7/20/55	53.	..	40 mg. hydrocortisone	Good
N. W.	44, M	4/15/55	36.	75	20 mg. prednisone	.....
		9/16/55	59.	..	15 mg. prednisone	Good
		11/18/55	38.	..	10 mg. prednisone	Fair
		12/30/55	19.	..	10 mg. prednisone	Relapse
		3/23/56	66.	82	15 mg. prednisone	Good
		4/13/56	72.	..	15 mg. prednisone	Good
R. W.	52, F	7/22/55	41.	63	.....	.....
		9/ 7/55	125.	..	40 mg. hydrocortisone	Good
		10/17/55	80.	..	30 mg. hydrocortisone	Good
		11/28/55	74.	..	20 mg. hydrocortisone	Good
		2/ 6/56	32.	..	20 mg. hydrocortisone	Fair
L. H.	49, F	9/ 6/55	2.1	61	.....	.....
		9/13/55	15.	..	.....	.....
		9/23/55	114.	85	30 mg. prednisone	Good
		11/18/55	134.	..	30 mg. prednisone	Good
E. S.	62, F	1/26/56	3.4	74	.....	.....
		2/14/56	0.	66	30 mg. prednisone	Poor
		2/22/56	16.	66	30 mg. prednisone	Fair
		3/ 1/56	69.	85	80 mg. hydrocortisone	Good
J. R.	45, F	10/25/55	18.	75	.....	.....
		11/ 2/55	34.	91	30 mg. prednisone	Good
		12/ 7/55	264.	..	20 mg. prednisone	Good
A. A.	64, F	10/31/55	43.	75	.....	.....
		11/ 8/55	74.	85	30 mg. prednisone	Good
		12/ 7/55	243	..	30 mg. prednisone	Good
T. C.	35, M	7/19/55	9.0	35	.....	.....
		8/18/55	25.	..	100 mg. hydrocortisone	.....
		8/22/55	34.	58	50 mg. prednisone	Good
		9/13/55	67.	74	15 mg. prednisone	Good
D. H.	26, F	6/22/55	48.	56	100 mg. cortisone	Good
M. H.	61, F	8/30/55	30.	..	25 mg. cortisone	Fair
		2/21/56	21.	60	150 mg. cortisone	Relapse

The data in patients with malabsorptive diseases or with low plasma carotene values are presented in greater detail in Tables III to VII. Table III shows the simultaneous improvement of plasma carotene and the coefficient of fat absorption in eight of ten patients with non-tropical sprue who received steroid therapy. In two of these patients the improvement was clearly noted within two weeks. (Fig. 3.) Two patients (D. H. and M. H.) also responded favorably but serial data were incomplete. Little or no improvement in either the coefficient of absorption or the plasma carotene occurred in two additional patients with steatorrhea (Table IV); the mechanism of the faulty fat absorption in these two cases was not known and, despite many

TABLE IV

RESISTANT STEATORRHEA—FAILURE TO IMPROVE DURING STEROID THERAPY

Date	Carotene (μg./100 ml.)	Coefficient of Absorption (per cent)	Steroid Dose (per day)	Clinical Status
G. H. 75, Male. Severe Steatorrhea and Gastric Hypersecretion				
7/25/55	48	78	.....	Fair
9/24/55	26	70	.....	Relapse
9/29/55	29	..	.....	Poor response
10/29/55	38	75	.....	Fair
3/28/56	77	66	30 mg. prednisone	Fair
B. W. 48, Male. Diarrhea, Steatorrhea, Acquired Hypogammaglobulinemia and Splenomegaly				
11/28/55	16	89	.....	Fair
12/15/55	10	80	30 mg. prednisone	Poor
12/22/55	4	..	30 mg. prednisone	Poor
1/ 9/56	16	69	100 units ACTH	Poor
1/18/56	12	33	100 units ACTH	Very poor
1/31/56	1.1	..	0	Very poor
3/16/56	3.4	..	0	Slightly improved

TABLE V

PLASMA CAROTENE IN SMALL BOWEL DISEASE AND ULCERATIVE COLITIS

Patient	Age and Sex	Disease	Coefficient of Absorption (%)	Plasma Carotene (μg./100 ml.)
Small Bowel Disease Other than Sprue				
L. G.	38, M	Postresection, short bowel with recurrent regional enteritis	10	31
		Several months later	65	42
C. P.	52, F	Postresection, blind intestinal loop	82	55
P. K.	20, M	Amyloid of small bowel, ileostomy	85	30
E. K.	47, M	Postresection, short bowel with ileocolitis	85	57
F. P.	57, M	Terminal ileitis	89	74
M. P.	35, M	Extremely short small bowel, postresection	10	18
L. S.	35, M	Regional enteritis, postresection	89	17
R. Z.	27, M	Ileocolitis	82	38
R. W.	28, M	Ileocolitis with cirrhosis	80	20
R. R.	41, F	Regional enteritis	..	23
G. A.	33, M	Regional enteritis with fistulas	41	49
B. D.	24, M	Regional enteritis	..	20
H. A.	42, M	Regional enteritis	99	38
I. R.	40, M	Recurrent regional enteritis, postresection	90	12
Ulcerative Colitis without Known Small Bowel Involvement				
M. N.	31, F	Ulcerative colitis	..	41
H. G.	25, F	Ulcerative colitis	..	54
A. S.	17, M	Ulcerative colitis	..	43
J. S.	21, M	Ulcerative colitis	93	26
C. S.	30, F	Ulcerative colitis	..	52

TABLE VI

PLASMA CAROTENE IN PANCREATIC AND LIVER DISEASE

Patient	Age and Sex	Disease	Coefficient of Absorption (%)	Plasma Carotene (μg./100 ml.)
Pancreatic Disease				
H. H.	50, M	Inoperable carcinoma, clinical steatorrhea	..	18
A. M.	42, M	Inoperable cystadenocarcinoma, steatorrhea	..	22
M. H.	59, M	Inoperable carcinoma, steatorrhea	53	52
G. O.	55, M	Inoperable carcinoma	88	65
G. A.	36, F	Chronic pancreatitis, severe	45	21
H. M.	66, F	Cystadenocarcinoma of pancreas	..	85
E. P.	58, F	Carcinoma of pancreas with metastases	..	110
F. S.	59, F	Hemochromatosis and mild fibrosis of pancreas	98	33
O. D.	35, F	Chronic pancreatitis, mild	98	28
E. K.	54, M	Carcinoma of pancreas, steatorrhea	68	47
		After 1 week of oral pancreatic extract	..	76
Liver Disease				
E. R.	44, F	Cirrhosis, partial pancreatectomy (11 yr.)	..	48, 23
M. A.	26, F	Cirrhosis, splenomegaly	..	47
E. R.	80, M	Cirrhosis	..	62
R. J.	33, F	Cirrhosis, portal hypertension	..	218
G. B.	21, F	Hepatitis, healing phase	..	126
F. S.	59, M	Hemochromatosis, cirrhosis	98	33
G. P.	52, M	Hepatitis, cholangiolitic	43	74
		Postoperatively, with biliary fistula	21	10
R. W.	28, M	Ileocolitis, cirrhosis	80	20

months of trial, no effective treatment could be found.

In advanced regional enteritis (Table v) the degree of steatorrhea occasionally was more severe than the plasma carotene would indicate, although the levels were normal only in two patients with mild disease. Only a few determinations were made in patients with ulcerative colitis and liver disease; here the plasma carotene seemed to correlate with the severity of the illness. In pancreatic disease with steatorrhea (Table vi) the plasma carotene was a useful index; but in carcinoma of the pancreas, despite the presence of widespread metastases, the plasma carotene level was normal in the presence of normal fat absorption.

In an attempt to differentiate low carotene levels caused by dietary depletion from those due to intrinsic absorptive defects, a few studies were made with oral carotene supplements. Twenty thousand units of carotene-in-oil administered daily for one week produced in most

patients a two- to threefold rise (Table VII); but in those with known absorptive defects the values did not return to normal. In two patients with liver disease and steatorrhea the plasma carotene values did not change.

TABLE VII
RESPONSE OF LOW PLASMA CAROTENE TO DAILY ORAL SUPPLEMENTS (20,000 U.) FOR ONE WEEK

Patient	Diagnosis	Plasma Carotene before Oral Dose	After Oral Dose (μg./100 ml.)
W. H.	Normal	70	158
A. W.	Dietary depletion	44	192
J. K.	Duodenal ulcer	57	93
C. S.	Ulcerative colitis	52	124
M. K.	Diarrhea without steatorrhea	54	152
R. H.	Dietary depletion	59	158
O. D.	Mild chronic pancreatitis without steatorrhea	28	77
L. S.	Postgastrectomy syndrome without steatorrhea	54	71
I. R.	Regional enteritis with steatorrhea	19	55
G. P.	Hepatitis, bile fistula	10	9
R. W.	Cirrhosis, ileocolitis and steatorrhea	25	25
B. W.	Steatorrhea and hypogammaglobulinemia	3	27
J. H.	Postsurgical short small bowel with probable steatorrhea	40	64
H. C.	Ileostomy dysfunction with steatorrhea	18	45
E. K.	Carcinoma of the pancreas with steatorrhea	47	44
J. W.	Regional enteritis with steatorrhea	16	22
D. J.	Non-tropical sprue	3	2

COMMENTS

The range of plasma carotene in the present normal series was slightly lower than the normal range reported by others. This is not unexpected since our patients without organic gastrointestinal diseases appeared for medical attention because of definite symptoms. Many patients were taking restricted diets as prescribed by their physicians. It is in this group that a screening test for abnormal fat absorption is of most value. The blood carotene determination was of definite aid in rapidly distinguishing a normal absorptive mechanism in 103 of the 110 patients. Analysis of dietary habits, fat balance studies, or response to oral carotene supplements in the remaining seven patients revealed a normal absorptive mechanism.

In patients with definite malabsorption of fat, the plasma carotene as a screening test was effective in fifty-one of fifty-eight determinations but was deceptive in three patients with postgastrectomy steatorrhea (Table VIII), two with mild steatorrhea accompanying regional enteritis, and in one with jaundice and steatorrhea attributed to hepatitis.

Assuming that blood carotene levels below 70 μg. per 100 ml. in the previously reported series

TABLE VIII
PLASMA CAROTENE IN POSTGASTRECTOMY STEATORRHEA

Patient	Age and Sex	Coefficient of Absorption (%)	Plasma Carotene (μg./100 ml.)
	Mild Steatorrhea		
G. L.	43, F	91	44
H. F.	72, F	85	72, 60
M. G.	47, M	88	124
E. T.	52, F	81	98
	Severe Steatorrhea		
G. A.	68, M	45	13
J. T.	50, M	68	27
M. S.	46, F		
	(9/27/55)	69	18
	(10/21/55)	79	32
	(10/29/55)	88	47

reflect dietary depletion, then the ranges of normal correspond fairly well to the present data. Only in one series [*25*] are the normal levels lower; in that study hospitalized patients served as controls but their dietary intakes were not recorded and in all probability this "normal" range is too low.

Low levels of blood carotene in celiac disease have long been known. Clausen and McCoord in 1938 [*28*] concluded that in patients on a normal diet a single blood carotene determination was informative as a screening procedure for the presence of steatorrhea. The present data certainly support this view. In a study of fecal fat and serum carotene in children Andersen and di Sant'Agnese [*33*] obtained similar results. In forty-two of forty-four children with celiac disease extremely low levels of serum carotene were noted when the patients were first hospitalized. Twenty-nine of this group had an elevated fecal fat excretion by chemical determination; a number of the others were eating little, hence the total output of fat in the stools was deceptively low. Perhaps calculation of the coefficient of absorption might have been more informative.

In the ten patients with classic sprue the diagnosis was first documented in most instances by

extremely low plasma carotene values. Similar findings have been noted by Cayer [*34*], Ingelfinger [*35*], Adlersberg [*36*] and others. Although some observers have found that low carotene levels persist despite clinical remission, this no longer holds true with steroid therapy. When steroids are given a rise in plasma carotene heralds a decrease in steatorrhea and a favorable clinical response, whereas lack of such a rise suggests that the steatorrhea may be due to other etiologic factors. On several occasions a fall in plasma carotene coincided with a period of relapse; high levels were maintained in the sprue syndrome under adequate therapeutic control. That in sprue carotene is absorbed more poorly than dietary fat is suggested by the extremely low levels of 0, 2, 3, 9 μg. per 100 ml. despite coefficients of fat absorption of 66, 61, 74, 69 per cent.

The phenomenon observed in certain cases of advanced regional enteritis, or in the presence of a surgically produced short small bowel requires another explanation. Here, although the plasma carotene was depressed it never reached the low levels of sprue. Despite fecal excretion of fat almost equalling intake, blood carotene levels of 31, 18 and 49 μg. were observed. A likely explanation may be that enough small intestine of normal absorptive capacity remains so that some carotene is absorbed. In a few patients with steatorrhea due to small bowel resection slight improvement was noted in the coefficient of absorption and plasma carotene during therapy with low fat diet and anticholinergic drugs, but neither reached normal values. Improvement of the blood carotene levels with similar therapy has been reported by Albright [*37*].

In pancreatic and liver disorders the present studies suggest that malabsorption of fat and carotene are approximately parallel, but only when the disease is extensive. The case of one patient, G. P., is of interest: With hepatitis simulating obstructive jaundice and a high fecal fat excretion, the plasma carotene was 74 μg. per 100 ml. Bile was observed in the duodenal contents at this time. After surgical construction of an external biliary fistula the coefficient of fat absorption and fecal urobilinogen fell to extremely low levels. After a few weeks the plasma carotene had decreased to 10 μg. per 100 ml. This case illustrates that in liver disease, if steatorrhea persists, carotene depletion will develop over an interval of time.

The etiology of a low plasma carotene requires individual investigation. High fever will depress carotene levels to a moderate degree. Dietary depletion is an important factor, particularly in the winter months when fresh vegetables are frequently absent from the diet. A low plasma carotene due to disease will most often be found in intrinsic defects of absorption, such as sprue and celiac disease, the postgastrectomy syndrome, advanced regional enteritis or other disorders of the bowel wall, or in the absence of adequate quantities of bile and pancreatic juice in the intestinal lumen. Established diagnostic methods will distinguish these various entities. The rapidity, technical ease and sensitivity of the plasma carotene determination, however, make it an excellent screening method to be used before the more elaborate and time-consuming procedures.

SUMMARY

1. The determination of plasma carotene is a simple, valuable screening test for steatorrhea.

2. Disorders other than steatorrhea presenting a low plasma carotene include high fever, poor dietary intake and liver disease.

3. The response of the plasma carotene is a useful guide to therapy in various malabsorptive disorders.

4. In patients with low plasma carotene levels a daily oral dose of 20,000 units of carotene-in-oil for seven days raised to normal the level of plasma carotene depleted by poor diet; in patients with absorptive defects normal levels were not achieved. This differing response may serve to distinguish further a borderline from a truly abnormal test.

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Interference of Abnormal Plasma Proteins with the Clotting Mechanism*

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IN a previous communication [*2*] the authors reported that precipitation of macroglobulin from the plasma of a patient with macroglobulinemia brought down with it both prothrombin and accelerator factors. Precipitation of these clotting factors also occurred when the macroglobulin was added to and reprecipitated from normal plasma.

In the following cases two types of precipitable proteins were found, a euglobulin and a cold precipitable fibrinogen-gamma globulin. These proteins were not macroglobulins but their precipitation effected the removal of prothrombin and accessory factors from the plasma in the manner of the macroglobulin previously described. The coprecipitation of these clotting factors with precipitable plasma proteins may be a general phenomenon and interference with the clotting mechanism by unusual plasma proteins may therefore occur more frequently than is appreciated [*3*].

CASE REPORTS

CASE 1. R. B., a twenty-eight year old man, entered the Cedars of Lebanon Clinic on January 16, 1956. Ten weeks previously he had had a laryngeal polyp removed, at which time plasma cells were found in the routine blood smears. A diagnosis of multiple myeloma was made which was confirmed by the finding of plasma cells in the bone marrow. At that time the patient received one blood transfusion to compensate for excessive blood loss. Three weeks later he received two more transfusions for anemia. During the four weeks prior to admission the patient noted considerable gum and nasal bleeding and on one occasion rectal bleeding. He lost 16 pounds, was pallid and tired easily. During this period he received meticorten. Three weeks prior to admission pain developed in the lower right ribs followed shortly by pain in the lower left ribs. During the ten-day period prior to admission the patient received three x-ray treatments bilaterally to the ribs.

The past history of the patient was non-contributory. On admission to the hospital he was pale, had swollen, bleeding gums and an enlarged spleen (4 cm.). The red cell count was 3.05 million per cu. mm., hemoglobin 9.0 gm. per cent, packed cell volume 28 per cent, white blood cells 1,300 per cu. mm. The differential count was polymorphonuclears 74 (stab forms 16), lymphocytes 20 and monocytes 6 per cent. There were 5 myeloma cells/100 white blood cells and marked rouleaux formation of the red cells. The sedimentation rate was 25 mm./hour (corrected Wintrobe). Prothrombin was 61 per cent and Lee-White clotting time was normal. The urine contained 3+ albumin and Bence Jones protein.

The patient received a whole blood transfusion on admission and a severe reaction developed which was treated with 20 units of ACTH intravenously and 100 mg. of benadryl.® The direct Coombs' test following the reaction was positive and cross matching of the blood was impossible due to a high titer of isoagglutinins. Following subsidence of the reaction the patient received a successful transfusion with packed red cells on two occasions.

During his hospitalization the patient received ACTH 20 to 40 units/day intravenously, meticorten® 10 to 20 mg./day for one week and urethane 3 gm./day for three days. The day prior to discharge he received 40 units of corticotropin zinc.

After the first transfusion of packed red cells there was no change in the red cell count and hemoglobin. After the second unit of packed red cells with concomitant steroid therapy there was a temporary rise of the red cell count to 4.1 million, the hemoglobin to 12.7 gm. per cent and the packed cell volume to 40 per cent. The sedimentation rate remained high, 38 mm./hour (corrected Wintrobe). The prothrombin was 100 per cent. Rouleaux formation persisted. In spite of the continued steroid therapy within four days after the second transfusion of packed cells the red cell count fell to 3.3 million, hemoglobin to 10 gm. per cent and packed cell volume to 35 per cent. Through-

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out the patient's hospitalization there was a leukopenia varying between 1,250 and 2,900 white blood cells per cu. mm. with polymorphonuclears 62 to 76 (stab forms 3 to 29), lymphocytes 12 to 36, monocytes 1 to 6 and eosinophils 0 to 5 per cent, and a thrombocytopenia (platelets 82,000 to 102,000).

Other laboratory studies were as follows: Cephalin flocculation test 1+ in 24 hours, 2+ in 48 hours; prothrombin consumption 95 per cent; no cold agglutinins in the serum; total serum protein 8.5 gm. per cent, albumin 3.5 gm. per cent, globulin 5.0 gm. per cent; blood serum chloride, sodium, potassium, creatinine, urea nitrogen, bilirubin, CO_2 combining power, alkaline phosphatase and cholesterol esters were normal, as was the bromsulphalein retention. Serum amylase was 46 units (normal 80 to 150 units). Cholesterol was 297 mg. per cent (normal by the method employed 150 to 260 mg. per cent). Blood culture was negative in 48 hours. The bone marrow was hyperplastic, with 95 per cent plasmablasts. The half-life of the red cells measured with chromium-51 was 17 days (normal 28 to 35 days).

During hospitalization the patient complained of blurred vision, which disappeared spontaneously in a week. The eye fundi were unremarkable. The nasal hemorrhages persisted, occurring each morning, but the patient felt much improved. He was discharged to the outpatient department on February 2, 1956, with the recommendation to continue ACTH therapy.

Case II. M. S., a fifty-four year old woman, entered the Cedars of Lebanon Clinic on April 11, 1956, with abdominal distention and edema of the legs of two months' duration. Since 1949 she had had intermittent swelling of the legs which recently had become constant but with varying severity. Two months prior to admission the patient first noticed abdominal swelling, which was accompanied by increased swelling of the legs, aggravation of a pre-existing bronchial asthma and decreased urine output. She tired easily and the abdominal swelling became progressively worse. In February, 1956, she had an attack of diarrhea lasting five days.

The patient had a past history of typhoid fever in childhood and a severe trauma in 1942 resulting in partial ankylosis of the left shoulder. In 1947 a diagnosis of cancer of the cervix was made, which was treated with radiation without recurrence of symptoms. She had had a prolonged period of excessive alcoholism in 1952 to 1953 and one month in 1955.

On admission the patient had rhonchi in the lungs. The abdomen was distended and a shifting fluid wave was present. There was no adenopathy. The liver edge was felt 2 cm. below the costal margin. The spleen was not palpable. There were numerous spider telangiectases on the chest, face and legs. There was 2+ pitting edema and extensive non-pitting edema of the legs. A diagnosis of Laennec's cirrhosis or possibly metastatic carcinoma was made.

The coagulation time, bleeding time, white blood cells, red blood cell count, platelet count, packed cell volume, serum uric acid, cholesterol esters, creatinine, glucose and alkaline phosphatase were normal, as were the protein-bound iodine and electrocardiogram. Prothrombin varied between 61 and 92 per cent. The sedimentation rate was 38 mm./hour (corrected Wintrobe). The serum urea nitrogen was 5 mg. per cent, serum cholesterol 136 mg. per cent. Serum total bilirubin was 1.11 and 1.06 mg. per cent, direct bilirubin 0.67 and 0.98 mg. per cent, indirect bilirubin 0.44 and 0.08 mg. per cent. Thymol turbidity was 20 units on two occasions and bromosulphalein retention was 41 per cent and 54 per cent in one hour. The cephalin flocculation test was 1 to 2+ in 24 hours and 2 to 3+ in 48 hours. Serum transaminase was 536 units (normal 10 to 40 units). Urine urobilinogen was 0.4 Ehrlich units. Total serum proteins were 6.7 and 8.1 gm. per cent, albumin 2.6 and 3.1 gm. per cent, globulin 4.1 and 5.0 gm. per cent. The ascitic fluid was devoid of abnormal cells and contained 1.4 mg. per cent protein. Paracentesis was performed three times. The patient was given vitamins. She was discharged to the outpatient department on May 7, 1956.

MATERIALS AND METHODS

Euglobulin precipitation: The patient's serum or plasma was diluted with eleven volumes (Case I) and twelve volumes (Case II) of distilled water. The resultant precipitate was centrifuged, washed three times with distilled water, suspended in water and dissolved by the addition of solid NaCl to a concentration of 0.9 per cent.

Euglobulin-free plasma: The diluted plasma, after the removal of the euglobulin precipitate, to which solid NaCl was added to a final concentration of 0.9 per cent.

Cryoprecipitation from plasma: The patient's plasma was frozen and stored for at least twelve hours, thawed at room temperature and refrigerated at 5°C. for four to twelve hours. The precipitate which formed was separated by centrifugation, washed and dissolved as described for euglobulin.

Cryoprecipitate-free plasma: The plasma after removal of the cryoprecipitate.

Cryoprecipitation from serum: The patient's serum was mixed with an equal volume of normal plasma and then treated in the same way as the patient's plasma.

Cryoprecipitate-free serum-plasma: The mixture of the patient's serum and normal plasma after removal of the cryoprecipitate.

Diluted whole plasma: The patient's plasma diluted with eleven volumes (Case I) and twelve volumes (Case II) of 0.9 per cent NaCl solution.

Euglobulin precipitated and redissolved whole plasma: The patient's plasma from which the euglobulin was precipitated by water dilution, the precipitate being redissolved in the diluted plasma by the addition of solid NaCl to 0.9 per cent final concentration.

Electrophoresis: Paper electrophoresis with a Durham type apparatus.

Spectrophotometric measurements: The optical densities of protein solutions were read at 279 λ in a Beckman DU spectrophotometer. Turbidimetric measurements were made at 600 λ in a Beckman DU instrument.

Specific viscosity measurements: Made as previously described [*2*].

Clotting factors: Prothrombin activity was measured by the one-stage Simplastin and the Ware-Stragnell [*16*] methods. Accelerator factors were measured by the previously described modification of the Ware-Stragnell method [*2*]. Factor v was measured by the Lewis-Ware one-stage method [*7*]. Recalcified clotting time was measured as previously described [*2*]. Parke-Davis bovine topical thrombin and Warner-Chilcott bovine fibrinogen were used as indicated.

RESULTS

Serum Proteins. In Case I the total serum protein was 8.5 gm. per cent (3.5 gm. per cent albumin and 5.0 gm. per cent globulin). In Case II the total serum protein was 8.1 gm. per cent (3.1 gm. per cent albumin and 5.0 gm. per cent globulin). Paper electrophoresis showed an increase in the gamma globulin in both cases.

Ultracentrifugation. In Case I the plasma had a component amounting to approximately 1 per cent of the total protein which sedimented at $S_{20} = 13$. This is consistent with normal figures [*10–13,15*]. Neither the cryoglobulin nor the euglobulin precipitate had components with sedimentation constants higher than 7. Ultracentrifuge studies were not made in Case II.

Viscosity. All plasma and serum samples had increased specific viscosities and the viscosity increased as the temperature decreased. (Table I.) Viscosity characteristics were not significantly altered by the removal of the cryoprecipitable protein fraction in Case I. Hence the viscosity characteristics presumably were not due to the cryoglobulin and probably not due to the macroglobulin which was present in too low a concentration to account for the results. In Case II the viscosity characteristics were closer to normal (Table I) but gained in significance since they occurred in a clinical condition commonly accompanied by unexplained hemorrhages.

Euglobulin. Precipitation and electrophoresis: In both cases the serum and plasma had strongly positive euglobulin reactions. In Case I dilution with eleven volumes of water precipitated 19 per cent of the blood proteins as euglobulin, measured spectrophotometrically by difference. The precipitate centrifuged down into a compact, highly viscous layer. Upon washing it became progressively more granular. Some of the viscous material was eluted by the wash water which could not be centrifuged clear. Chilling the diluted plasma decreased the time of centrifugation necessary to separate the precipitate but did not affect the total amount obtained. Chilling of the wash water eluate for several hours permitted its separation by centrifugation.

TABLE I
SPECIFIC VISCOSITIES OF PATIENTS' SERUM AND PLASMA

Sample	Specific Viscosity		
	37.5°C.	20°C.	4°C.
Normal serum	0.615	0.679	0.688
Normal plasma	0.869	0.879	0.900
Case I:			
Serum (1)*	1.170	1.261	1.390
Serum (2)*	1.208	1.339	1.450
Whole plasma	1.650	1.830	2.170
Cryoprecipitate-free plasma	1.655	1.830	2.090
Case II:			
Serum	1.090	1.198	1.290
Whole plasma	1.185	1.310	1.560

* Samples taken on different days.

In Case II dilution with twelve volumes of water was necessary to precipitate completely the euglobulin, which amounted to 5 per cent of the blood protein, measured spectrophotometrically by difference. No peculiarities were encountered in centrifuging or washing the viscous precipitate.

The 0.9 per cent NaCl solutions of the serum and plasma euglobulins in both cases all had single electrophoretic gamma globulin components.

Solubility of the euglobulin: Solubility of the euglobulin in both cases was influenced by both salt concentration and temperature (Table II), the effects of which were interrelated. The addition of salt-free human albumin to 2.7 gm. per cent redissolved the precipitates. The cryoprecipitability of the euglobulin was therefore determined in part by the salt and albumin concentration.

Effect of precipitation of euglobulin on clotting factors: In order to evaluate the effect of the globulin precipitation, comparisons of clotting factor

activity were made in euglobulin-free plasma, diluted whole plasma and euglobulin precipitated and redissolved whole plasma. The mechanics of the precipitation had no effect on clotting factor activity since there were no differences between the activity of the saline diluted whole plasma and euglobulin precipitated and redissolved whole plasma. However marked differences were observed in the euglobulin-free plasma as compared with whole plasma.

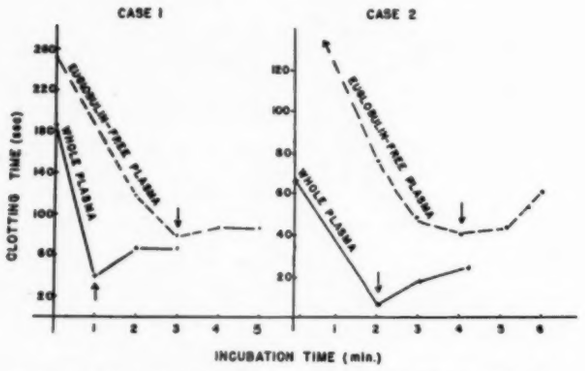

FIG. 1. Coprecipitation of prothrombin and accelerator factors with euglobulin.

In Case I precipitation of the euglobulin from the patient's plasma brought down with it prothrombin and accelerator factors. (Fig. 1.) Euglobulin-free plasma had a clotting time by the modified Ware-Stragnell method which was eight times as long as that of the saline diluted whole plasma. This was indicative of the removal of prothrombin. In addition, the euglobulin-free plasma required twice the incubation time of saline diluted whole plasma to reach maximum thrombin formation, indicative of a reduction in accelerator factors. Factor V was not measured and since there was no special treatment of the samples necessary for its preservation, the accelerator activity found was probably due to factor VII.

In Case II factor V activity was reduced from 70 per cent in the whole plasma to 17 per cent in the euglobulin-free plasma. The results in an aged sample showed coprecipitation of both prothrombin and accelerator factors, probably factor VII, with the euglobulin. (Fig. 1.) The euglobulin-free plasma had a minimum clotting time twice as long as that of the saline diluted whole plasma and required three times the incubation time of the diluted whole plasma to reach maximum thrombin formation.

Clotting characteristics of the euglobulin precipitates: In Case I prothrombin and accelerator factors were detectable in the plasma euglobulin precipitate. (Table III.) The euglobulin precipitate from the serum was striking in that it also contained prothrombin and accelerator factors and the concentration of prothrombin was of the same order as that found in the precipitate from plasma. Since the prothrombin consumption was complete (5 per cent activity in the serum) the prothrombin present in the serum euglobulin precipitate was also present in the native plasma but in a form unavailable to the clotting mechanism, perhaps due to combination with the euglobulin.

TABLE II
INTERRELATIONSHIP OF SALT CONCENTRATION AND TEMPERATURE ON SOLUBILITY OF EUGLOBULIN

Sample	NaCl %	Optical Density 600 λ		
		37.5°C.	20°C.	4°C.
Case I:				
Cryoprecipitate-free plasma	0.20	0.090	0.092	0.085
	0.10	0.180	0.227	0.316
	0.05	0.260	0.302	0.388
	0.025	0.255	0.290	0.365
Case I:				
Serum	0.20	0.095	0.100	0.103
	0.10	0.075	0.089	0.155
	0.05	0.151	0.220	0.350
	0.025	0.160	0.192	0.265
Case II:				
Serum	0.30	0.062	0.075	0.090
	0.20	0.075	0.091	0.128
	0.10	0.089	0.123	0.173
	0.05	0.098	0.125	0.180

In Case II prothrombin and accelerator factors were detectable in the plasma euglobulin. (Table III.) Factor V activity was also found, but since conditions of testing the euglobulin solutions were of necessity different from those of the plasma samples, no comparisons were made. Results with the serum euglobulin solutions suggested that clotting factor activity might be present but were equivocal. Cryoprecipitates were found only in Case I.

Cryoprecipitation and electrophoresis: Plasma which was frozen, then thawed and refrigerated developed a dense, white, viscous precipitate

TABLE III

CLOTTING CHARACTERISTICS OF EUGLOBULIN PRECIPITATES FROM SERUM AND PLASMA

Sample	Test	Plasma Precipitate		Serum Precipitate		Interpretation
Case I	Recalcified clotting time	240 sec.		No clot		Clotting factors present in euglobulin from plasma
	+ Fibrinogen	No clot		900 sec.		Trace of thrombin in serum euglobulin
	+ Thrombin	Few shreds immediately		No clot		Trace of fibrinogen in plasma euglobulin
	One-stage prothrombin + fibrinogen	30 sec.		30 sec.		Prothrombin present in serum and plasma euglobulins
	Ware-Stragnell prothrombin	25 sec.		39 sec.		Prothrombin and possibly accelerator factors present in serum and plasma euglobulins
	Accelerator factors (modified Ware-Stragnell test)	Incubation Time (min.)	Clotting Time (sec.)	Incubation Time (min.)	Clotting Time (sec.)	Accelerator factor(s), probably factor VII, present in serum and plasma euglobulins
		0	94	0	>240	
		1	38	1	179	
		2	32	2	84	
		3	23	3	142	
		4	23			
		5	20			
Case II	+ Fibrinogen	No clot				No thrombin in euglobulin
	+ Thrombin	No clot				No fibrinogen in euglobulin
	One-stage prothrombin + fibrinogen	258 sec				Prothrombin present in euglobulin
	Ware-Stragnell prothrombin	143 sec				Prothrombin and possibly accelerator factors present in euglobulin
	Accelerator factors (modified Ware-Stragnell test)	Incubation Time (min.)	Clotting Time (sec.)			Accelerator factor(s), probably factor VII, present in euglobulin
		0	143			
		1	106			
		2	52			
		3	29			
		4	20			
		5	17			

which started separating within four hours. The cryoprecipitate centrifuged down into a semi-solid jelly which in one sample (January 20, 1956) separated spontaneously on further refrigeration into an upper viscous layer (fraction 1) and a lower white, amorphous solid layer (fraction 2). The viscosity of fraction 1 appeared to be considerably less than that of the original precipitate.

The cryoprecipitate from a second plasma sample (February 3, 1956) which was frozen immediately and precipitated thirteen days later failed to separate into two fractions. Washing eluted a portion of the precipitate which migrated electrophoretically as gamma globulin. The washed precipitate in 0.9 per cent NaCl solution had both a gamma globulin and a fibrinogen component and other lesser components. The solution of the precipitate was refrigerated for twelve days when it was again

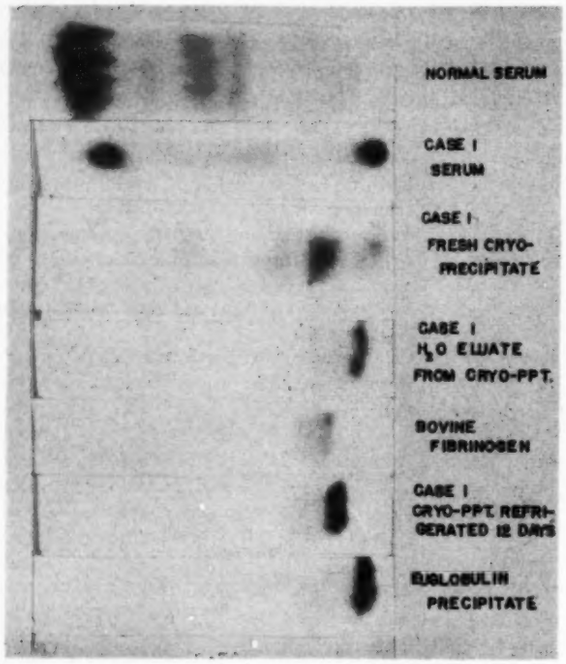

FIG. 2. Normal serum, reading from left to right: albumin, γ_1 globulin, γ_2 globulin, β globulin and γ globulin. Case 1, serum shows increased γ globulin. Case 1, fresh cryoprecipitate shows fibrinogen and γ globulin and lesser amounts of other components. Case 1, water eluate from cryoprecipitate shows γ globulin only. Case 1, cryoprecipitate refrigerated twelve days shows a single component with mobility between fibrinogen and γ globulin. Euglobulin precipitate shows γ globulin only.

studied by electrophoresis. At this time it showed a single component which migrated mid-way between fibrinogen and gamma globulin, suggesting the possibility that on storage in the cold a complex formed between the gamma globulin and the fibrinogen. (Fig. 2.)

Euglobulin was demonstrable in the cryoprecipitate-free plasma, indicating that the euglobulin and the cryoglobulin fractions were not identical. The fibrinogen of the whole plasma, as determined by the Jacox method [*4*], was 750 mg. per cent. After cryoprecipitation only 370 mg. per cent remained in the cryoprecipitate-free plasma. Of the 380 mg. per cent presumably precipitated with the cryoglobulin, about 140 mg. per cent could be accounted for by the same method in the redissolved cryoprecipitate. Six per cent of the total plasma protein was represented in the cryoprecipitate by measurement of spectrophotometric difference.

No cryoglobulin was demonstrable in the patient's serum. However a cryoprecipitate was obtained from an equal mixture of the patient's serum and normal plasma which was routinely frozen, thawed and chilled. The serum-plasma mixture freed of this cryoprecipitate gave a positive euglobulin test. The precipitate in 0.9 per cent NaCl solution had major electrophoretic components in the fibrinogen and gamma globulin regions with lesser components in the albumin and beta globulin regions. Further study is needed to determine the significance of these lesser components.

Clotting characteristics of the cryoprecipitates: The cryoprecipitates contained three clotting factors, fibrinogen, prothrombin and accelerator factors. (Table IV.) The sample (January 20, 1956) which separated spontaneously into two fractions gave further separation of the clotting factors. Fraction 1, the viscous liquid layer, contained fibrinogen and prothrombin. There was not a sufficient sample to determine accelerator factors. Fraction 2, the amorphous solid, contained prothrombin and accelerator factors but no fibrinogen.

The cryoprecipitate from the sample of February 3, 1956 had certain unusual features. The water eluate of the precipitate had prothrombin activity. Refrigeration of the saline solution of the washed precipitate for twelve days resulted in a marked reduction in both fibrinogen and prothrombin activity which occurred simultaneously with the electrophoretic evidence of appearance of a component with mobility between the fibrinogen and gamma globulin fractions.

The cryoprecipitate from the mixture of the patient's serum and normal plasma had fibrinogen, prothrombin and accelerator factor activity. (Table V.) The cryoprecipitate-free mixture had lower prothrombin and accelerator factor activities than did a similar unprecipitated mixture.

COMMENTS

Case 1, an instance of plasma cell myeloma, is unusual in that both a cryoprecipitate, which appeared to be a complex of fibrinogen and gamma globulin, and a euglobulin, which was a gamma globulin, could be separated from the plasma. No macromolecules could be identified in the solutions of the separated proteins and only a trace of a fast sedimenting component ($S_{20} = 13$) was present in the plasma. Neither of the unusual proteins was, therefore, a macroglobulin. Although a positive euglobulin test has been considered presumptive evidence of a macroglobulin [*15*], it is increasingly evident that

TABLE IV

CLOTTING CHARACTERISTICS OF CRYOPRECIPITATES FROM PLASMA OF CASE I

Sample	Test	Fraction 1	Fraction 2		Total Cryoprecipitate		Water Eluate from Total Cryoprecipitate	Interpretation
January 20, 1956	+ Thrombin	Immediate clot	No. Clot					Fibrinogen in fraction 1 but not in fraction 2
	+ Fibrinogen		No clot					No thrombin in fraction 2
	Ware-Stragnell prothrombin	42 sec.	87 sec.					Both fractions contain prothrombin and possibly accelerator factors
	Accelerator factors (modified Ware-Stragnell test)		Incubation Time (min.)	Clotting Time (sec.)				Accelerator factor(s), probably factor VII, present in fraction 2
			2	374				
			4	280				
			6	120				
			8	114				
			10	76				
			12	54				
February 3, 1956	Recalcified clotting time				55 sec.		No clot	Total cryoprecipitate contains clotting factors
	+ Thrombin				3 sec.		No clot	Total cryoprecipitate contains fibrinogen, water eluate does not
	+ Fibrinogen						No clot	Water eluate does not contain thrombin
	One-stage prothrombin				41 sec.		360 sec.*	Both fractions contain prothrombin
	Ware-Stragnell prothrombin				23 sec.		31 sec.*	Both fractions contain prothrombin and possibly accelerator factors
	Accelerator factors (modified Ware-Stragnell test)				Incubation Time (min.)	Clotting Time (sec.)		Accelerator factor(s), probably factor VII, present in total cryoprecipitate
					2	207		
					3	150		
					4	143		
					5	153		
					6	97		
February 3, 1956 Tested after 12 days refrigeration	+Thrombin				37 sec. defective			Fibrinogen activity reduced
	One-stage prothrombin + fibrinogen				126 sec.			Prothrombin activity reduced in presence of added fibrinogen

* Discrepancy in values probably due to shortage of fibrinogen, which is added in the Ware-Stragnell Test.

macroglobulins may, but do not always, precipitate as a euglobulin [*1,5,8,9,14*] and that other proteins may have the solubility characteristics of euglobulins.

In the case of liver damage, Case II, the abnormal protein was a euglobulin which migrated as a gamma globulin. The viscosity data did not suggest the possibility of more than a trace of macroglobulin and, in view of our experiences in Case I, no ultracentrifuge studies were undertaken.

The most significant feature of this study was the interference by the unusual proteins in the clotting mechanism. Such interference was previously described for macroglobulin [*2*]. In the present study it was effected by proteins of normal size, indicating that disturbances in the clotting mechanism may be induced by such proteins as well as by macroglobulins. Precipitation of the euglobulin from either plasma or serum in Case I was accompanied by precipitation of prothrombin and accelerator factors

TABLE V

CLOTTING CHARACTERISTICS OF CRYOPRECIPITATE FROM CASE I SERUM PLUS NORMAL PLASMA

Test	Results		Interpretation
+ Thrombin	Immediate clot		Fibrinogen present
One-stage prothrombin	133 sec.		Prothrombin present
Ware-Stragnell prothrombin	146 sec.		Prothrombin and possibly accelerator factors present
Accelerator factors (modified Ware-Stragnell test)	Incuba-Time (min.)	Clotting Time (sec.)	Accelerator factor(s), probably factor VII present
	0	360	
	2	170	
	3	117	
	4	258	

which were identifiable in the precipitates. The finding of prothrombin activity in the serum euglobulin fraction approximating that found in the plasma euglobulin when prothrombin activity was 100 per cent and prothrombin conversion was 95 per cent suggests that the euglobulin may have combined with prothrombin prior to blood clotting. The fact that no decrease in prothrombin and accelerator factors could be detected in the plasma after cryoprecipitation, although both of these factors could be identified in the solutions of the precipitates, is consistent with such a thesis, in this instance in respect to the cryoprecipitable protein. On precipitation and resolution, the clotting factors were released and became measurable. These observations raise interesting speculations concerning disturbances in the plasma prothrombin levels and how compensation or even overcompensation could result in an unbalanced and unstable clotting mechanism.

The thesis of combination of the euglobulin and clotting factors is supported by a comparison of two measurements, clotting characteristics and electrophoresis. Electrophoretically, the plasma cryoprecipitate consisted of two fractions, fibrinogen and gamma globulin. After twelve days of refrigeration these two components migrated as one electrophoretic component mid-way between fibrinogen and gamma globulin.

A cryoprecipitate also was obtained from a mixture of normal plasma and the patient's serum. Since such a precipitate did not form from either component separately, it is inferred that the unusual proteins present could associate or complex with other proteins. These may be prothrombin, accelerator factors, fibrinogen or a variety of other proteins yet to be defined. It would also appear that cold precipitability may develop as the result of a combination of some unusual protein with fibrinogen.

The results in Case II were not as startling as those in Case I but they offered further support to the postulated theory. They are of added importance since they were observed in cirrhosis of the liver, which is commonly associated with hemorrhagic tendencies. Again the coprecipitation of prothrombin and accelerator factors from plasma with the euglobulin was demonstrated and these factors could be identified in the isolated euglobulin. It is suggested that the bleeding tendency in some cases of liver damage may result in part from the operation of the postulated mechanism.

We have recently been able to demonstrate the presence of small amounts of prothrombin activity in cryofibrinogen precipitates from normal oxalated human plasma. Further study of this phenomenon is in progress. However on the basis of present evidence it appears that coprecipitation of prothrombin and accessory factors is to be expected with the precipitation of any plasma protein.

SUMMARY

1. Two types of precipitable blood proteins, a euglobulin and a cryoprecipitable protein complex occurring in a case of multiple myeloma, and a euglobulin found in a case of cirrhosis of the liver have been studied.

2. The cryoprecipitable protein complex appeared to consist of fibrinogen and gamma globulin, neither of which was precipitable alone. The two components under certain conditions migrated electrophoretically as a single component of intermediate mobility. This was associated with a marked reduction in fibrinogen and prothrombin activity of the precipitate.

3. Both the euglobulins and the cryoprecipitable protein complex coprecipitated with prothrombin and accessory factors. Neither of these components was a macroglobulin.

4. Complexing of unusual plasma proteins with clotting mechanism proteins may occur more generally and lead to interference with the clotting mechanism in a variety of diseases.

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Hazard of Severe Infections in Splenectomized Infants and Children*

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INCREASING experience with splenectomy has emphasized the therapeutic value and freedom from ill effect of the procedure when carried out for well defined indications. Because of this attitude of security, it seems important to call attention to a group of cases in which serious and at times fatal infection has occurred in the splenectomized patient.

In a previous publication [*1*], two children were reported in whom an overwhelming and fatal illness occurred with high fever, severe prostration and coma, sixteen months and two weeks, respectively, after splenectomy for Cooley's anemia. Examination of the literature at that time revealed that King and Shumacker [*2*] had reported five infants under the age of six months with congenital spherocytic anemia. In four of these children either meningitis or overwhelming meningococcemia developed within five weeks to three years after operation, with one fatality. The fifth child died of a rapidly fatal febrile illness a few days after discharge.

The present report represents an extension of our initial observation indicating a heightened susceptibility to severe infection in a group of infants and children in whom the spleen had been removed for a variety of conditions mostly of a hematologic nature. While these untoward circumstances in the immediate and remote postoperative period cannot be unequivocally attributed to splenectomy, the relationship seemed more than fortuitous and sufficiently impressive to warrant recording, especially during an era when this procedure is so frequently recommended.

The cases to be reported fall into several categories: those associated with meningitis, acute pericarditis and sepsis, and a group consisting of acutely ill children in whom the course was so fulminating as to preclude the detection of a specific etiologic agent. Case histories are given for each group. Only fragmentary laboratory observations were available for the fulminating cases (XIII, XIV, XVI and XVII).

CASE REPORTS

Patients with Meningitis. CASE I. N. W. was born on June 15, 1952. There was a gradually increasing enlargement of the liver, spleen and lymph nodes dating from the age of three months. On October 19, 1953, the spleen was removed for "hypersplenism" on the basis of a peripheral pancytopenia and a hyperplastic bone marrow affecting all cellular elements. From this time until the present illness the child was well except for massive enlargement of all superficial lymph nodes. Repeated biopsies and bone marrow studies revealed no diagnostic pattern of any known disease.

After discharge from the hospital the child remained well until eight days prior to admission. When he awoke he was delirious and had a temperature of 105°F. A day later slight stiffness of the neck was noted. The fever persisted and he was treated with antibiotics. Stiffness of the neck became more marked and he was admitted to The New York Hospital on January 7, 1955. Physical examination revealed redness of the throat; the liver was felt about three fingerbreadths below the costal margin, and (surprisingly) the lymph nodes had almost completely receded in size. Nuchal rigidity was marked. The hemoglobin was 9.5 gm. per cent, the white blood cells 50,000 per cu. mm., with 83 per cent polymorphonuclear neutrophils. The spinal fluid was purulent, contained 5,000 cells per cu. mm. and 100 per cent polymorphonuclears. The smear revealed gram-positive diplococci. The culture

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of the spinal fluid grew out pneumococci. Vigorous treatment with penicillin and sulfadiazine resulted in the patient's complete recovery. With this improvement, the lymph nodes again increased in size. The attack of meningitis occurred fourteen months after splenectomy.

CASE II. L. G. was born on April 11, 1932. Early in life he was found to have severe Cooley's anemia. A splenectomy was performed on July 9, 1934, because of excessive transfusion requirements. After splenectomy the hemoglobin was maintained at 7.5 gm. with no transfusions until April, 1942. At that time two transfusions were given in preparation for a minor surgical procedure. The patient remained well until September 17, 1945, when he was admitted with evidences of meningitis. On the day of admission he returned from school with a generalized headache and vomiting. His neck became markedly rigid. The hemoglobin was 6.9 gm. per cent, the red cells 2.2 million, the white blood cells 32,000 per cu. mm., with 83 per cent polymorphonuclear leukocytes. The lumbar puncture on admission revealed cloudy fluid containing 25,000 white blood cells, 100 per cent of which were polynuclear cells. Culture of the spinal fluid revealed E. coli. The patient responded to penicillin and sulfadiazine therapy and was discharged on the twenty-seventh hospital day. The attack of meningitis occurred eleven years after splenectomy.

CASE III. B. J. was born on March 30, 1951. He had a splenectomy on June 26, 1953, because of the need for repeated transfusions. Anemia had been observed from the eighteenth day of life. The bone marrow had consistently shown an erythroblastic hypoplasia but the other cellular elements were normal. Without transfusions hemoglobin levels dropped to 6 gm. per cent, but the white count, myeloid cells and platelets were normal. Based on the isolated defect of red cell function the condition was diagnosed as pure red cell (chronic congenital aregenerative) anemia. After splenectomy, transfusion needs were moderately reduced.

He was admitted to a local hospital on January 7, 1954, with a history of fever of twenty-four hours' duration, inflammation of the throat and vomiting. The temperature on admission was 105°F.; nuchal and back rigidity and a Kernig's sign were present. The spinal fluid contained 1,053 cells with 66 per cent polynuclears. The hemoglobin was 6.5 gm. per cent, the red count 1,920,000, the white count 12,500 per cu. mm. with 58 per cent polynuclears. The spinal fluid and blood culture grew out pneumococcus. Antibiotic therapy was actively administered and with supportive treatment including transfusions the child made a complete recovery. Prior to this admission he had had a moderate number of upper respiratory infections. He had completed a course of cortisone in connection with the anemia about three weeks before the onset of the meningitis. The interval between the splenectomy and meningitis was six months.

CASE IV. R. B., a six year old boy, had a traumatic rupture of the spleen in the summer of 1944 which required splenectomy. During the course of his convalescence he received several blood transfusions. About three weeks later chills and fever developed and he was readmitted to the hospital. The blood smears were filled with quartan malarial parasites. With atabrine® he made an uneventful recovery. One of the donors gave a history of having had malaria seventeen years previously. As there had been no other contact a presumptive diagnosis was made of malaria transmitted by blood transfusion although no parasites could be demonstrated in the donor's blood. On April 6, 1945, the patient was admitted to the Bellevue Hospital; he was acutely ill, had a temperature of 106°F., and complained of pain in the left leg. The white blood count was 24,800 per cu. mm. with 89 per cent polymorphonuclear neutrophils. Blood culture revealed type 23 pneumococcus. No focus was found in the lungs, sinuses or mastoids. After a drop to normal, following sulfadiazine and penicillin treatment, the temperature rose again to 104.4°F. Signs of meningitis were apparent. The spinal fluid was cloudy with 2,000 cells and type 23 pneumococcus was isolated. The patient recovered after intensive treatment with penicillin and sulfadiazine. Nine months after discharge he returned again with pneumococcal meningitis, type 12, from which he recovered after treatment with appropriate antibiotics. The intervals between splenectomy and the attacks of meningitis were approximately one year and eighteen months, respectively.

CASE V. D. E. was born on October 8, 1946. He was admitted to the hospital on January 25, 1954, for evaluation of marked splenic enlargement complicating pure red cell (congenital aregenerative) anemia, diagnosed early in infancy. The splenomegaly was interpreted as a response to excessive hemolysis in connection with repeated transfusions. Ashby studies revealed decreased survival of donor cells. Splenectomy was performed on April 26, 1954, after which transfusion requirements were reduced.

On December 15, 1955, at nine years of age, he complained of headache, nausea and vomiting and his temperature rose to 104°F. He was treated with penicillin and improved. Ten days later the temperature rose to 105°F. and despite antibiotic therapy the headache became more intense and stiffness of the neck was noted. On admission the signs were those of meningitis. There were 1,710 cells per cu. mm. in the spinal fluid with 80 per cent polymorphonuclear cells. The smear revealed gram-positive diplococci which were identified as pneumococci on culture. With penicillin and sulfadiazine therapy he recovered completely. The meningitis occurred twenty months postsplenectomy.

CASE VI. A. M., an eight and one-half year old boy, had recurrent infections of the ears and bronchi for several months. Examination revealed an enlarged spleen, leukopenia and diminished granulocytes. Splenectomy was performed on May 28, 1953 on the basis of a presumptive diagnosis of splenic neutropenia. After the operation the incidence of infection was reduced and the white count rose together with increased numbers of polymorphonuclear neutrophils. On October 1, 1954, the patient complained of headache and vomiting. Penicillin was given orally and he improved. At 1 A.M. on October 3, he was found comatose and his neck was stiff. The spinal fluid was cloudy with a total cell count of 4,900 per cu. mm. On smear, gram-positive diplococci were noted which were later identified as pneumococci. He died on October 4, twenty-four hours after admission. The interval between splenectomy and the fulminating meningitis was about sixteen months.

CASE VII. J. B. was born on December 12, 1944. A splenectomy was performed in 1953 for "hemolytic anemia" after which no further transfusions were required. She was hospitalized on January 20, 1956, because of chills, headache, backache, vomiting and a temperature of 102°F. The symptoms began six days before admission but subsided twenty-four to forty-eight hours after with the use of terramycin.® On admission physical examination revealed marked nuchal rigidity and other meningeal signs. The blood count showed a hemoglobin of 16.5 gm. per cent, red blood count 5,100,000, white blood count 31,000 per cu. mm. with 85 per cent polymorphonuclear neutrophils. The spinal fluid was cloudy with 6,520 white cells per cu. mm. and 89 per cent neutrophils. The culture revealed H. influenzae, type B. With the administration of chloramphenicol and sulfadiazine the temperature subsided and meningeal signs disappeared. The child was asymptomatic on discharge. The interval between splenectomy and the meningitis was three years.

Patients with Pericarditis. The children in this group had severe Cooley's anemia. The spleen had been removed in each instance as a means of reducing transfusion requirements. This objective was attained in varying degree in each case. The high white counts must be evaluated in terms of the erythroblastemia which is greatly exaggerated after splenectomy in this disease.

CASE VIII. J. F. was born on October 11, 1937. He had a splenectomy on November 30, 1938. He was well until mid-January 1951 at which time he had a bout of diarrhea. This cleared and he was well until two weeks later. On February 4, 1951, at the age of thirteen years, he had acute onset of severe pain in the epigastrium and left lower anterior chest which was aggravated by breathing. On admission he was afebrile but in pain and short of breath. The heart was enlarged to the left and an apical systolic murmur was present. No friction rub was heard at this time. The hemoglobin was 11.5 gm. per cent. The white blood count 36,000 per cu. mm. with large numbers of normoblasts. On the second day of hospitalization the temperature rose to 38.5°C. At this time an electrocardiogram was taken which revealed an ST elevation in leads I and II and AVF. On the third day a friction rub was heard in the mitral area. An increase in the size of the cardiac silhouette which persisted for three weeks was interpreted as due to pericardial effusion. The pericardial friction rub was heard until the fourth week and then disappeared. By the third week the ST segments again became isoelectric. By the fourth week the T waves, which had been low in AVF and umbilicated in I, II and V2-5, returned to normal size and contour. The interval between splenectomy and pericarditis was twelve years.

CASE IX. J. N. was born on April 21, 1944. He had a splenectomy on November 20, 1951. He was first admitted to the hospital at the age of ten months with a hemoglobin of 3.2 gm. per cent. On October 7, 1953 sharp substernal pain developed which radiated to the right shoulder and increased on respiration. The temperature rose to 103°F. He was treated with penicillin and erythromycin. Twenty-four hours later his temperature was normal but the pain persisted. He was examined in the out-patient department on October 9, 1953, because of the pain. The heart sounds were normal and no friction rub was heard. The electrocardiogram showed slight elevation of the ST segment in lead II which had not been present previously which was consistent with the changes seen in acute pericarditis. He became asymptomatic four days later. An electrocardiogram on October 13 showed elevation of the ST segments in leads I, II and V_5.

On January 8, 1955, he again had an attack of sudden severe substernal pain radiating to the back and associated with difficulty in breathing. He was asymptomatic in twenty-four hours following antibiotic therapy. When he was seen in the clinic ten days later he was afebrile and no friction rub was heard. The electrocardiogram, however, showed elevation of the ST segment in leads II, III, V_5 and V_6. The ST elevation in lead II was still present on January 25, 1955. The electrocardiogram was normal on February 18, 1955. The intervals between the attacks of pericarditis and splenectomy were two and three years, respectively.

CASE X. F. G. was born on May 8, 1945. He had a splenectomy on March 30, 1953, because of increasing difficulty in maintaining adequate hemoglobin levels with repeated transfusions. Except for an attack of malaria traced to a transfusion, the requirements for blood were subsequently reduced. On January 7, 1955, at the age of nine years and nine months, he was

admitted to the hospital with acute pericarditis. Ten days prior to admission he had a profuse nose bleed. The next day the temperature rose to 102°F.; four days later he complained of headache, malaise and vomiting. On the morning of the day of admission a severe sharp pain in the lower anterior chest grew in intensity and radiated to the back and left shoulder. The pain was intensified by respiration and was somewhat relieved by sitting. On admission his temperature was 38.2°C. which became normal the next day. Cardiac examination revealed a harsh blowing systolic murmur over the precordium with a point of maximal impulse 10 cm. from the mid-sternal line. The blood count showed a hemoglobin of 7 gm. per cent. White blood count was 22,500 per cu. mm. with 81 per cent polymorphonuclear neutrophils and many nucleated red blood cells. The electrocardiogram showed an elevation of the ST segments in leads I, II, V_5 and V_6. The T wave in lead III, previously positive, had become negative. No evidence of fluid was noted. The patient was treated with achromycin.® By January 14 the electrocardiogram had returned to normal. The interval between the splenectomy and pericarditis was twenty-two months.

CASE XI. S. S. was born on April 30, 1938. She had a splenectomy on December 1, 1949. In October, 1950, she had a fever of 104°F., sore throat and loose cough followed by precordial and left anterior chest pain which was aggravated by inspiration. These symptoms gradually subsided over a one-week period. On December 25, 1950 she complained of severe anterior chest pain. The next day the temperature rose to 102°F. On December 29, the chest pain became more intense and she was admitted to the hospital. The temperature was 38°C., and examination revealed a harsh to-and-fro friction rub over the entire precordium but maximal along the left sternal border. Fluoroscopy revealed an enlarged cardiac silhouette with good pulsations everywhere except near the right diaphragm where they were distinctly diminished. The corrected white blood count was 20,000 per cu. mm. with 66 per cent polymorphonuclear neutrophils. The electrocardiogram showed low voltage of the QRS complex and umbilication of T wave in lead II, suggesting a diagnosis of pericarditis with effusion. The pain disappeared within a few days but low grade fever and the friction rub persisted. On January 3 and 19, 1951, fluoroscopy revealed diminished pulsation along both cardiac borders indicative of increased pericardial effusion. The electrocardiogram continued to show low voltage of the QRS complex and flattening of the T waves. Aureomycin was given from time of admission until January 30, 1951, without apparent effect either on the pericarditis or on the low grade fever. On February 5, 1951, the T waves became more nearly normal in contour although the low voltage QRS persisted. Within a few days the friction rub was no longer audible and fluoroscopy showed no evidence of pericardial effusion. By February 20, 1951, the electrocardiogram had returned to normal and she was discharged three days later. The interval between the splenectomy and pericarditis was one year.

CASE XII. A. DiB. was born on January 20, 1936. He had a splenectomy on July 21, 1953. On October 8, 1953, he complained of severe anterior chest pain radiating through to the back which wakened him from sleep. There was an antecedent history of upper respiratory infection two weeks before. The pain was somewhat lessened by sitting. Respirations were difficult and limited by the chest pain. Slight cyanosis of the hands and feet was noted. The temperature rose to 39.4°C. shortly after admission. The hemoglobin was 6.3 gm. per cent, and the corrected white blood count 10,000 per cu. mm., with 74 per cent polynuclear neutrophils. A friction rub was heard in the fourth left intercostal space. The electrocardiogram the next day showed an elevation of the ST segment in leads I, II, AVF and V_4–V_6. Pain and friction rub were gone by October 11, 1953. Electrocardiograms showed progressive changes with persistent ST elevation and varied stages of depression or inversion of T waves. By October 19, leads were normal but some T wave changes in V leads persisted.

On November 12, 1954, he was again wakened from sleep with severe anterior chest pain aggravated by respiration. The temperature was 38.6°C. The electrocardiogram showed slight elevation of the ST segments in leads I and II. The hemoglobin was 6.8 gm. per cent, the corrected white cell count was 23,000 per cu. mm. with 63 polynuclears. There were 700 nucleated red cells per 100 white blood cells. Treatment with bed rest, codeine and oxygen resulted in rapid alleviation of the symptoms and of cyanosis. He was discharged on the twentieth hospital day. The electrocardiogram showed resolution and on January 7, 1955, it was normal except for evidence of left ventricular hypertrophy.

On May 18, 1955, he again awoke with severe left chest pain radiating to the back and left arm. He had suffered an upper respiratory infection three weeks previously. No friction rub was heard. The ST segment elevation noted on the electrocardiogram on admission returned to normal on discharge on May 25. Minor T wave changes remained which became normal by the time the next electrocardiogram was taken in the clinic five months later.

These attacks of pericarditis occurred three months, sixteen months and almost two years, respectively, following splenectomy.

Patients with Fulminating Infection and Sepsis. These patients were observed either in the immediate or remote period following splenectomy. A characteristic feature was the suddenness and overwhelming nature of the infection accompanied by septicemia in several cases. In three instances (B. R., S. S., D. B.) death

overtook the patient within twenty-four hours after the onset with a similar clinical pattern and before appropriate laboratory tests could be undertaken to identify the causative agent.

CASE XIII. C. A. was born on January 12, 1938. He had a splenectomy on March 3, 1939 because of severe Cooley's anemia with increased transfusion needs. He had several hospital admissions mainly for transfusions. On his out-patient visit on October 1, 1940, he had a slight fever but was not acutely ill. The temperature gradually rose to 41°C. when he was admitted on the morning of October 3 comatose, dyspneic and with marked pallor. The heart was enlarged on percussion to the anterior axillary line with a loud systolic murmur over the precordium. The liver was down to two fingerbreadths above the iliac crest on the right. The hemoglobin was 4 gm. per 100 cc. of blood, the red count 1,720,000 per cu. mm. The high white count of 450,000 per cu. mm. was due mainly to nucleated red cells. Despite energetic treatment the child died several hours after admission. The blood culture before and after death showed B. coli communis. Necropsy revealed only the characteristic evidences of advanced Cooley's anemia. The interval between splenectomy and this infection was nineteen months.

CASE XIV. D. B. was born on July 20, 1943. He was admitted to the hospital on November 14, 1943, with intermittent vomiting, pallor and hepatosplenomegaly. A diagnosis of severe Cooley's anemia was made for which periodic transfusions were subsequently given to maintain a hemoglobin range of 7 to 10 gm. per 100 c.c. After 1948 these levels became progressively difficult to attain despite greater frequency of transfusions. Splenectomy was accordingly performed on April 16, 1949, at the age of six years, with striking clinical improvement and reduced transfusion needs. The patient awoke on August 4, 1950, complaining of headache. Muscular spasm and rigidity developed, he vomited and complained of intense generalized pain. He was admitted to the hospital at 1:10 P.M., semi-comatose and in acute respiratory distress. The temperature was 104.6°F., the pulse 180 per min. respirations 64 per min., the lungs showed coarse bubbling rales. He became extremely cyanotic, failed to respond to stimuli, and died one hour after admission. Necropsy performed two hours later revealed evidence of generalized hemosiderosis and hemochromatosis. Fibrosis of the heart was not present, and the lungs showed only focal areas of atelectasis and emphysema. No abnormalities of the brain were present either grossly or microscopically. Except for a small amount of iron pigment the adrenals were normal. The postmortem findings provided no explanation for the clinical features. The interval between splenectomy and this illness was sixteen months.

CASE XV. B. S. was born on December 4, 1948. She had a splenectomy in 1954 because of traumatic rupture of this organ. Two days before the present admission she complained of abdominal pain. The next day the temperature was 102°F. and rose to 107°F. during the course of twenty-four hours. The child became rapidly lethargic and on admission on October 7, 1955, she was in a semi-coma. Examination showed no abnormalities except a moderate postnasal drip. The abdominal and hematologic examinations were normal. The blood showed a hemoglobin of 12.5 gm. per cent, and a white blood count of 20,400 per cu. mm. with 97 per cent polynuclear neutrophils of which 59 per cent were band forms. X-rays of teeth, neck, chest, skull, spine and knees were all negative. The nose, throat and blood cultures grew out alpha streptococci. Therapy included chloramphenicol and penicillin to which the organisms were sensitive, hydrocortisone and other supportive measures. The child became afebrile seven days after admission and remained so throughout the hospital course. During the active phase of the disease the white blood cells rose to 85,000 per cu. mm., with 72 per cent band forms. Several small sterile purpuric spots appeared on the second to third days after admission persisting for five to ten days. The interval between splenectomy and this illness was approximately one year.

CASE XVI. B. R. was born on September 3, 1939. She was known to have severe Cooley's anemia and had a splenectomy at The New York Hospital on June 4, 1954, because of increased transfusion needs and massive enlargement of this organ. She made an uneventful recovery and was discharged eleven days later. On June 17, 1954, while at home, she suddenly appeared lethargic and a fever developed with the temperature rising to 106°F. A small area of exudate was noted on one tonsil and penicillin was given. She was admitted to a local hospital complaining of pain in the right lower chest. She appeared in respiratory distress and oxygen was administered. The uncorrected white blood count was 126,000 per cu. mm. with 400 nucleated red cells for every 100 white cells. She quickly lost consciousness and died shortly thereafter with right sided clonic contractions. Postmortem culture from the heart blood grew out gram-negative rods of the coliform group resembling A. aerogenes. Necropsy revealed bilateral adrenal interstitial cortical hemorrhage, acute tonsillitis, hyperplasia of the bone marrow and hemosiderosis of the pancreas, lymph nodes, kidneys and pituitary. There were no abnormalities of the heart, lungs or central nervous system to account for the clinical picture. The interval between splenectomy and this illness was thirteen days.

CASE XVII. A. V. was born on November 3, 1937. She had a splenectomy on April 25, 1951. The original

diagnosis of Cooley's anemia was later changed to thalassemia–sickle cell disease on the basis of blood findings, hereditary and electrophoretic patterns. Transfusion needs, which had been excessive, were reduced to two to three month intervals following the operation. In 1953, the occurrence of right upper quadrant pain led to the removal of a gall-bladder containing stones. In 1954, she was hospitalized for right lower lobe pneumonia complicated by a pulmonary infarction possibly related to intravascular blocking by sickle cells. Five days before the present admission on December 14, 1955, an illness developed characterized by the acute onset of chills and fever without localizing signs but with severe generalized bone pain. There was temporary improvement following the administration of antibiotics. She became critically ill and was admitted with a temperature of 40.2°C. Abdominal and bone pain were marked. The hemoglobin was 7.5 gm. per cent, the red blood count 2,100,000 per cu. mm., the white count (corrected) 15,000 per cu. mm. with 56 per cent polynuclear neutrophils. The lungs showed a few fine rales at the right base posteriorly, the heart was enlarged and a loud systolic murmur was heard over the precordium most marked at the apex and pulmonary areas. The liver was non-tender and five fingerbreadths below the costal margin. She appeared pale, icteric and withdrawn. Salmonella typhimurium was cultured from her blood. Pyoarthritis of both elbows developed on the eighth day and aspiration of the joints revealed the same organism. Treatment with a variety of antibiotics, principally chloramphenicol, terramycin and streptomycin, resulted in gradual subsidence of the fever. Amelioration of the arthritic complications followed aspiration and injection of antibiotics. The interval between splenectomy and the sepsis was four years and nine months.

Case xviii. F. G. was born on October 7, 1931. He had a splenectomy on May 4, 1935, because of advanced Cooley's anemia. This was followed by several admissions for transfusions to maintain hemoglobin levels. On December 1, 1935, he complained of fever, headache and vomiting; epistaxis and dyspnea set in. The temperature rose to 105.5°F. and he was admitted to the hospital on December 5. Physical examination showed rapid and labored breathing, pallor, a loud systolic murmur and a liver palpable just above the umbilicus. All the joints seemed to be tender and swollen. The hemoglobin was 5 gm. per cent, the red blood cells 1,770,000, the white count 19,500 per cu. mm. with 84 per cent polynuclears. The blood culture showed a heavy growth of pneumococcus type 1, which remained positive after December 14. No petechiae were found. Vigorous treatment with anti-pneumococcus type 1 serum was initiated, transfusions were given without avail and the patient died on December 26, 1935, with a diagnosis of acute bacterial endocarditis and suppurative endocarditis due to pneumococcus type 1. The interval between the splenectomy and the terminal illness was seven months. Necropsy confirmed the diagnosis of acute vegetative endocarditis of the mitral and tricuspid valves.

Case xix. S. S. was born on May 28, 1948. She had a splenectomy on July 22, 1955, for thrombocytopenic purpura of four years' duration. She had been on a therapeutic regimen including cortisone without improvement. She had been given 40 mg. meticorten daily for three weeks before admission and penicillin prophylactically. She received blood during the operative procedure which she tolerated well and left the operating room in good condition. On July 23, one day postoperatively, at 9:20 A.M. the doctor was called to see the patient who was pulseless and with blood pressure too low to record. She had a mottled appearance with labored respirations and a temperature between 106 and 108°F. Energetic treatment was administered including hydrocortisone. Cheyne-Stokes respirations developed and the patient died at 11:10 A.M. A spinal tap showed clear fluid. No permission for autopsy was obtained. The interval between splenectomy and death was twenty-four hours

ANALYSIS OF CASES

Clinical Types of Infection and Bacteriology. It will be noted in Table I that the infections fall into several well defined categories: meningitis (seven cases), acute pericarditis (five cases), acute endocarditis (one case), sepsis (three cases) and a group consisting of acutely ill patients in whom the course was so fulminating as to preclude the detection of a specific etiologic agent (Cases xiv, xvi and xix).

Of the eleven cases in which bacterial diagnosis was possible, the pneumococcus was the most frequent offender (six cases). Also isolated were E. coli (two cases), S. typhimurium (one case), alpha streptococcus (one case) and H. influenzae (one case). It is noteworthy that the pneumococcus was the predominant organism in the group with meningitis (five of seven cases). In one case (Case iv) successive attacks of meningitis were due to different strains of pneumococcus (cf. with two cases in Table II of Gofstein and Gellis). Also significant was the occurrence of influenzal meningitis, which has a peak incidence between six and twelve months of age, in a child of eleven years (Case vii). It is also of interest that the majority of the infections occurred between the months of October and March.

Examination of the individual histories reveals that in the majority of instances an apparently

TABLE 1

CASES OF SEVERE INFECTION FOLLOWING SPLENECTOMY (PRESENT SERIES)

Case No.	Patient	Age at Splenectomy	Indication for Splenectomy	Type of Infection	Bacteriology	Interval between Splenectomy and Infection	Remarks
I	N. W.	16 mo.	Secondary hypersplenism	Meningitis	Pneumococcus	14 mo.	Recovered
II	L. G.	2 yr.	Cooley's anemia	Meningitis	E. coli	11 yr.	Recovered
III	B. J.	2 yr. 3 mo.	Pure red-cell anemia	Meningitis	Pneumococcus	6 mo.	Recovered
IV	R. B.	6 yr.	Traumatic rupture	Meningitis	Pneumococcus, type XXIII Pneumococcus, type XII	1 yr. 18 mo.	Recovered Recovered
V	D. E.	8 yr.	Pure red-cell anemia	Meningitis	Pneumococcus	20 mo.	Recovered
VI	A. M.	8½ yr.	Splenic neutropenia	Meningitis	Pneumococcus	16 mo.	Died
VII	J. B.	11 yr.	Hemolytic anemia	Meningitis	H. influenzae	3 yr.	Recovered
VIII	J. F.	13 mo.	Cooley's anemia	Acute benign pericarditis	.....	12 yr.	Recovered
IX	J. N.	7½ yr.	Cooley's anemia	Acute benign pericarditis	.....	2 yr. 3 yr.	Two attacks; recovered
X	F. G.	8 yr.	Cooley's anemia	Acute benign pericarditis	.....	22 mo.	Recovered
XI	S. S.	11 yr.	Cooley's anemia	Acute benign pericarditis	.....	1 yr.	Recovered
XII	A. DiB.	17 yr.	Cooley's anemia	Acute benign pericarditis	.....	3 mo. 16 mo. 2 yr.	Three attacks; recovered
XIII	C. A.	14 mo.	Cooley's anemia	Sepsis	B. coli communis	19 mo.	Died
XIV	D. B.	6 yr.	Cooley's anemia	Sepsis ?	Undetermined	16 mo.	Died
XV	B. S.	6 yr.	Traumatic rupture	Sepsis	Alpha streptococcus	1 yr.	Recovered
XVI	B. R.	14 yr.	Cooley's anemia	Sepsis	Coliform group ?	13 days	Died
XVII	A. V.	14 yr.	Thalassemia-sickle cell disease	Sepsis	S. typhimurium	4½ yr.	Recovered
XVIII	F. G.	3½ yr.	Cooley's anemia	Acute bacterial endocarditis	Pneumococcus, type I	7 mo.	Died
XIX	S. S.	7 yr.	Thrombo-cytopenic purpura	Undiagnosed	Unknown	24 hr.	Died

TABLE II

SUMMARY OF CASES OF SEVERE INFECTION FOLLOWING SPLENECTOMY IN INFANTS AND CHILDREN (PREVIOUSLY REPORTED)

From the Literature (author, reference, year)	Age at Splenectomy	Indications for Splenectomy	Type of Infection	Bacteriology	Interval between Splenectomy and Infection	Remarks
Gruber, Redner and Kogut, 1951 [20].	14 hr.	Thrombocytopenic purpura	Sepsis	?	21 days	Died nine days after onset of infection
King and Shumacker, 1952 [2].	Case I 3 wk.	Hereditary spherocytosis	Meningitis	N. meningococcus	1 yr.	Recovered
	Case II 3 wk.	Hereditary spherocytosis	Meningitis	?	5 mo.	Recovered
	Case III 15 days	Hereditary spherocytosis	Meningococcemia	N. meningococcus	8 mo.	Died few hours after admission
	Case IV 6 mo.	Hereditary spherocytosis	Meningitis	H. influenzae, type B	3 yr.	Recovered
	Case V 2½ mo.	Hereditary spherocytosis	Sepsis	Undetermined	3 wk.	Died on third hospital day
Evans, Waters and Loman 1954 [21].	7 wk.	Hereditary spherocytosis	Meningococcemia	N. meningococcus	6 mo.	Recovered
Simpkiss and Cathie 1954 [22].....	14 mo.	Thrombocytopenic purpura	Septicemia	Not stated	2 mo.	Died
Walter and Chaffin 1955 [23].....	17 mo.	Gaucher's disease	Meningitis	Pneumococcus	7 mo.	Died
	3½ yr.	Splenic neutropenia	Upper respiratory infection	Not stated	13 mo.	Died
Gofstein and Gellis 1956 [3].....	6 yr.	Hereditary spherocytosis	Meningitis	Pneumococcus, type XIX	3 mo.	Died
	6 mo.	Idiopathic thrombocytopenic purpura	Meningitis	Pneumococcus, type VI	15 mo.	Recovered
			Meningitis	Pneumococcus, type XXIII	21 mo.	Recovered
	1 yr.	Idiopathic thrombocytopenic purpura	Meningitis	Pneumococcus, type XXIII	5 mo.	Recovered
			Meningitis	Pneumococcus, type IX	15 mo.	Recovered
	25 mo.	Cooley's anemia	Sepsis	Pneumococcus	3½ yr.	Died

healthy child, after a short prodromal period, became seriously ill with one of the clinical patterns described in this series. Occasionally such episodes occurred in a child who either before (Case VI) or after splenectomy (Case XVII) had been subject to infections of the ears, upper respiratory tract and pulmonary passages. In several cases, notably of meningitis, the flagrant

clinical features were preceded by several days of illness during which antibiotics were administered with seeming improvement.

In the cases of pericarditis (eight attacks in five children), all of which occurred in patients with severe Cooley's anemia, no specific organism was isolated. The clinical features and laboratory tests correspond to the syndrome of acute benign or idiopathic pericarditis reported in increasing numbers particularly in adults. Each of the patients experienced sudden intense pain and pressure substernally and across the upper and lower anterior chest radiating to the back and shoulders. The pain was aggravated by breathing or motion and somewhat relieved by the sitting position. Leukocytosis, fever, a pericardial friction rub, occasionally with evidences of effusion, were significant features. The electrocardiogram showed the characteristic changes consisting initially of an elevation of the ST segments with upright T waves. These persisted for a varying length of time with the later development of low, flat or inverted T waves. The tendency to recurrence in this condition was observed in Cases IX (two attacks) and XII (three attacks).

Age at Splenectomy: Interval between the Operation and Infection. The age at which splenectomy was performed extended from thirteen months to seventeen years. The appearance of severe infection in the postsplenectomized period shows, therefore, no preference for the young infant as stressed by King and Shumacker [*2*].

The interval between the operation and infection ranged between one day to twelve years, with the majority of episodes two years or less (80 per cent). The shortest periods were twenty-four hours and thirteen days postoperatively (Cases XIX and XVI, respectively), both characterized by a fulminating course with temperatures ranging from 106° to 108°F. and a fatal outcome. While the patient (Case XIX) may have suffered a cerebral complication based on hemorrhage following removal of the spleen for thrombocytopenic purpura, the clinical aspects paralleled those of other patients in whom death followed closely after the onset of symptoms.

Conditions for which Splenectomy was Performed. In the majority of cases the spleen was removed as a means of reducing transfusion requirements in patients with severe Cooley's anemia or its combination with sickle-cell disease (eleven cases) and in two cases of pure red-cell (chronic congenital aregenerative) anemia (Cases III and V). In the patient (Case XIX) with thrombocytopenic purpura the condition had persisted for a prolonged period and medical treatment had been exhausted. In patients presumed to have a hyperactive spleen producing either pancytopenia (Case I) or neutropenia with chronic infection (Case VI), removal of the spleen resulted in improvement of the peripheral blood picture. More important in the thesis of a relationship between splenectomy and infection were the two well patients (Cases IV and XV) in whom the spleen had been removed following traumatic rupture.

Pathology of the Spleen and Other Organs. Histopathologic examination of the spleen and often of a liver section following operation and of other organs at postmortem in the fatal cases revealed no evidence of unsuspected conditions responsible for subsequent infection. In every case a definitive preoperative diagnosis could be made on the basis of the clinical course, bone marrow and other laboratory studies which was corroborated by subsequent tissue examinations when these were available.

Gamma Globulin Concentration. The partition of serum proteins by electrophoresis in severe Cooley's anemia provided data bearing on the relation of gamma globulin concentration to splenectomy. The observations recorded in Table III show that eight splenectomized patients in the present series gave no evidence of failure to synthesize gamma globulin. Regarding 0.6 to 1.2 gm. per 100 ml. of gamma globulin and 12 to 16 per cent (paper electrophoresis) as within the normal range, it will be observed in Table III that the concentration of gamma globulin exceeded the normal in patients with such diverse infections as pneumococcal meningitis (Cases I and V), acute benign pericarditis (Cases VIII to XII) and septicemia due to S. typhimurium (Case XVII).

It is of interest that in patients with Cooley's anemia concentrations of gamma globulin exceeded the normal, with somewhat higher values in those patients who had undergone splenectomy. In the sixteen children with intact spleens the mean concentration was 1.71 ($\pm$0.52) gm. per 100 ml. of serum with a range from 0.94 to 2.69 gm. as compared with 2.3 gm. ($\pm$0.57) in fourteen splenectomized patients with a range from 1.12 to 3.16 gm. It may be that the lower levels in the former are due to the larger number of younger children who were not yet eligible for splenectomy in whom the gamma globulin is

TABLE III

CONCENTRATION OF SERUM PROTEINS (PAPER ELECTROPHORESIS) IN GROUP OF SPLENECTOMIZED PATIENTS WITH INFECTION

Case No.	Albumin (Per cent total protein)	Globulins (Per cent total protein)				Total Protein (Gm./100 ml.)	Gamma Globulin (Gm./100 ml.)
		Alpha-1	Alpha-2	Beta	Gamma		
I	47.0	1.3	10.7	17.1	25.3	7.9	2.0
V	35.5	2.7	9.7	9.5	42.6	8.0	3.40
VIII	39.8	4.7	7.9	11.7	36.0	8.1	2.92
IX	44.3	4.0	9.3	13.0	29.4	8.5	2.50
X	47.3	3.2	8.8	9.2	31.5	7.8	2.44
XI	48.7	3.7	9.1	10.3	28.2	8.9	2.50
XII	49.8	3.3	7.3	11.3	28.3	8.9	2.51
XVII	41.7	3.3	9.8	11.2	34.0	8.0	2.72
Normal	57.4 [*24*]	4.2	8.5	14.0	15.9	7.75 ± 0.52 [*25*]	0.6–1.2

found in lesser concentration because of shorter duration of the disease.

Antibody Response Following Splenectomy. Dr. Susan Hadley of the Department of Medicine studied the antibody response in a small group of patients with severe Cooley's anemia, following a provocative dose of diphtheria toxoid. She noted no relationship between the presence or absence of the spleen and the titer of antibody, and that the highest titer occurred in a splenectomized patient.

COMMENTS

Table II summarizes the earlier series reported by King and Shumacker [*2*] as well as those cases in which serious and often overwhelming infection is mentioned as a complication by various authors of recent papers dealing with splenectomy. The four cases reported by Gofstein and Gellis [*3*] included in this table occurred in a group of 107 cases of splenectomized children under ten years of age, and demonstrated the proneness to pneumococcic infections, especially meningitis. This compilation does not constitute an exhaustive survey of the literature but serves rather to emphasize a specific hazard of splenectomy which is more fully documented in the cases under present consideration. (Table I.) Cole, Majarakis and Limarzi [*4*], for instance, mention pericarditis as a fatal complication in two patients, each three months after splenectomy, one with myeloid metaplasia of the spleen, the other with hypoplastic anemia, but the age and other details of the infection are not given.

One of the important functions of the spleen is its contribution to the defense mechanisms of the body. These are implied in the capacity for antibody formation and those factors involved in the natural and acquired resistance to bacterial and protozoal infection. Notwithstanding increasing numbers of individuals who have been subjected to splenectomy scant evidence has been given in published reports of heightened susceptibility to infection. In a recent series of 140 consecutive splenectomies, Miller and Hagedorn [*5*] have encountered no sequelae based on infection observed in the present report. Also in a study by Rousselot and Illyne [*6*], patients in whom the spleen has been removed for traumatic rupture showed no alteration in growth, development and predisposition to infection. Doan [*7*] comments that in his experience of more than 1,000 splenectomies in both children and adults he has not observed increased susceptibility to infection.

That serious infections have been so infrequently encountered is the more noteworthy in view of the large body of experimental evidence demonstrating the part played by the spleen in defense. This organ contains both the macrophage system whose cells exert a phagocytic activity and lymphocytes which are a source of antibody formation. Perla and Marmorston [*8*] have summarized in an exhaustive work numerous experimental observations which clearly focus attention on the spleen as an essential instrument in defense and natural resistance. In their own studies they found that removal of

the spleen in certain animal species depresses the natural resistance to acute and chronic infections. In rats and mice free of latent infections splenectomy depresses resistance to Bacterium enteriditis infection. They also demonstrated that the rat infected early in life with Bartonella muris recovers and remains well. Splenectomy subsequently breaks down the acquired resistance to the latent infection with the development of severe anemia.

Nearly fifty years ago Luckhardt and Becht [*9*] demonstrated that when emulsions of spleen from dogs receiving goat red blood cells intravenously were injected into the peritoneal cavity of normal dogs specific hemolysins were produced. From this they concluded that antigen accumulated in the spleen in detectable amounts. It has also been assumed that the function for antibody formation ascribed to the spleen is transferred to other organs following splenectomy. It is possible, however, to demonstrate a specific depression of this function following splenectomy by selecting the conditions of the experiments. Thus Rowley [*10*] showed that the splenectomized rat responds with a very low circulating antibody titer after the intravenous injection of sheep erythrocytes in contrast to good levels if introduced by other routes. In a subsequent study [*11*] he found that using the same antigen and mode of administration, twelve of fourteen patients who had had a splenectomy eight days to forty months previously failed to respond with a significant hemolysin titer as compared with the increased antibody response in individuals with an intact spleen.

In a recent paper dealing with the biochemical determinants of infection, Dubos [*12*] stated that "many types of substances, procedures or accidents have been found capable of bringing about conditions under which latent microorganisms can manifest their potential pathogenicity and cause overt disease." The case histories and related data in the present report suggest that removal of the spleen constitutes a condition which is capable in terms of this author of "provoking latent microorganisms into activity." The precise mechanisms responsible for this phenomenon cannot be categorically stated but the studies already mentioned support the thesis that severe infection following splenectomy is more than circumstantial and deserves earnest consideration.

The salient features of the case histories in the present series may now be interpreted against this background of experimental observation and opinion. It will be noted that the range in age at the time of splenectomy extends over the entire period of infancy and childhood and is not restricted to infants under the age of six months as had been previously suggested [*2*]. What is of interest is the frequency of serious infection in splenectomized infants and children as compared with the relative paucity in the adult. In the past ten years at The New York Hospital only one serious infection occurred in 225 consecutive splenectomized adult patients (over twenty years of age). This was in a fifty-six year old woman in whom pneumococcic meningitis developed one month after splenectomy for acquired hemolytic anemia. This experience compares with fourteen serious infections in fifty splenectomized children in the same institution, an incidence of 28 per cent. Four patients of the latter group, 8 per cent, succumbed in the particular episode of fulminating infection. It should be emphasized that in a group of comparable patients with severe Cooley's anemia and intact spleens, infections of the nature described in this report did not occur.

The striking difference between these two groups may stem from the normally increased resistance to infection with maturity which is high-lighted by the effects of splenectomy. Variation in susceptibility at different age periods is exemplified by the greater susceptibility of children than of the adult to H. influenzae bacteremia, tracheobronchitis due to influenzae and the staphylococcus, and pneumococcus peritonitis associated with ascites. The relation of the age of the subject to susceptibility to infection is an intriguing one. Baumgartner [*13*] presented contributory evidence to support the concept of "serological maturity" to explain the increased resistance of the adult over the child. This stems, according to this author, from the exposure to latent infections in childhood and of "physiological changes concomitant with his increasing years and not related to his previous infections. These changes would allow the production of specific organs of defense, antibodies which differ qualitatively and quantitatively from those produced in earlier life. The net result might be an increased resistance."

The lessened resistance following splenectomy may have been responsible for the occurrence of influenzal meningitis in a child of eleven years

(Case VII), a condition most common under one year of age. In a case not included in this series development of overwhelming chickenpox one month after splenectomy in a child of twelve years with severe Cooley's anemia was regarded as a major reason for the fatal outcome.

While the majority of cases in this series (eleven of nineteen) were patients with Cooley's anemia (including one case of thalassemia–sickle cell disease), other hematologic conditions are represented in this series. More significant because of their freedom from previous diseases are the two patients with traumatic rupture of the spleen (Cases IV and XV). Case IV combines several features which illustrate the underlying hypothesis applicable to the entire series, namely that the spleen maintains a state of acquired resistance to latent infection with a flare-up following its removal. The attack of malaria three weeks after splenectomy in this child following transfusion from a donor in whom the disease had occurred seventeen years before can be explained on a postulated protective role of the spleen in this condition. Of the factors of natural and acquired immunity to malaria the former is probably of lesser importance. Defense in this disease depends to a large extent on the concentration of the parasites in the spleen, among other organs, where they are destroyed by the reticuloendothelial cells [*14*]. One of the essential protective mechanisms which can be assumed to have been operative in the asymptomatic donor was thereby lost to the patient when the spleen was removed. While it is true that this sequence of transfusions from an asymptomatic donor often results in post-transfusion malaria regardless of splenectomy, the role of the spleen in this case cannot be entirely disregarded.

Two consecutive attacks of meningitis with different strains of pneumococcus in this patient and of single attacks in other cases offers additional support to the loss of specific resistance and protective influence exerted by the spleen. No explanation can be offered, however, for the clinical pattern of the disease such as the frequency of meningitis, sepsis or pericarditis.

The frequency of episodes of infection in late autumn and winter observed in this series of cases is of interest for several reasons. This seasonal incidence may play an etiologic role in connection with the observations of Reith and Squier [*15*] who in a study of routine blood cultures of apparently healthy persons found that they were more frequently positive during the months when upper respiratory infections are prevalent. In their comprehensive review of the experimental and clinical aspects of bacteremia, Bennett and Beeson [*16*] delineate various mechanisms that are mobilized when microorganisms enter the circulation. They point out that the majority of bacteria cleared from the blood after a single intravenous injection can be found most commonly in the liver and spleen, especially in the macrophages of the reticuloendothelial system. While complex mechanisms are involved in the reaction between the invading agent and the host, one of these probably relates to the role of the spleen in trapping organisms during transient invasion of the blood stream in the individual who is a carrier.

In recent years a form of acute pericarditis has been recognized which does not fall into one of the previously established categories and has been variously termed benign, non-specific, idiopathic or primary. It is usually ascribed to a non-bacterial viral etiology. Despite its frequency in adults this condition has been less commonly described in children [*17*]. The occurrence of eight attacks of acute benign pericarditis in five splenectomized children with Cooley's anemia is therefore worthy of special consideration. While the signs varied considerably, the clinical symptoms and electrocardiographic changes were typical of this recently described syndrome of pericardial inflammation. Although absent in a comparable group of fourteen children with intact spleens, pericardial effusion has occasionally been observed in Cooley's anemia in non-splenectomized cases [*18*]. The preponderance of this condition in the splenectomized group cannot be explained except by a state of increased susceptibility following splenectomy. Hemosiderosis with iron deposition in the pericardium and adjacent structures seems an unlikely inciting factor since the same condition prevails in the non-splenectomized group. This pathologic state cannot, however, be entirely discounted and may exert a contributory influence.

The lowered resistance to serious infection was not associated with a deficiency of serum gamma globulin. (Table III.) In the group with Cooley's anemia both splenectomized and non-splenectomized children showed increased concentrations of these proteins with significantly higher

values in the former. This is probably due to the older age of the splenectomized patient and the frequently progressive impairment of liver function found in this disease. The elevated values for the entire group (Table III) corresponded to some extent to children recently described [*19*] with hypergammaglobulinema who were entirely susceptible to infection. No further analogies can be made, however, because of the modest rather than excessively high levels of gamma globulin in their patients and the lack of chronicity of infections in the majority of patients in the present series.

The difficulty of demonstrating the importance of the spleen in immunologic responses was reflected in the failure to find differences in antibody titer in several splenectomized and nonsplenectomized children with Cooley's anemia who were subjected to injections of diphtheria toxoid. It is possible that depressed responses in the splenectomized individual requires the presence of the antigen in the blood stream which can only be accomplished experimentally by intravenous injections [*11*].

The fact that the majority of serious infections occurred within a two-year span following splenectomy provides a clue to clinical management. While it is obviously impractical to follow up splenectomized children for prolonged periods, the necessity for close supervision for several years postoperatively becomes obligatory. With the possibility that fulminating and occasionally fatal infections may supervene, such patients should necessarily receive immediate and energetic treatment in the event of sudden and severe illness. The routine administration of continuous prophylactic antibiotic treatment is attended by the difficulty of providing an effective drug with a sufficiently broad spectrum to encompass every variety of infection and by the possible emergence of resistant strains of common pathogens. Since the most common organism in this and other series is the pneumococcus it may be necessary to revive vaccination procedures for protecting the splenectomized child.

SUMMARY

A series of nineteen cases of severe and often fulminating infection, six terminating fatally, in children following splenectomy is presented. Except for two cases of traumatic rupture of the spleen, the major indication for splenectomy was based on the needs arising from an established blood disorder.

The infections fell into several well defined categories: meningitis, acute benign pericarditis (in patients with Cooley's anemia), acute endocarditis and sepsis. In the cases in which bacterial diagnosis was possible pneumococcus was the most frequent offender and of the clinical types, meningitis was most common. Pneumococcic meningitis predominated in this and other reports.

In the majority of cases the interval between splenectomy and infection was two years or less, with a range from one day to sixteen years. The age at splenectomy extended from thirteen months to seventeen years.

There was no diminution in the concentration of gamma globulin in these patients.

The cases described in this paper, together with current reports of a similar nature, suggest more than a random association between splenectomy and susceptibility to infection. An extensive experimental background implicates the spleen in fundamental processes relating to resistance to infection.

The sample reported in this paper is avowedly small in comparison with the ever increasing number of splenectomies. Nevertheless, while the benefits accruing from splenectomy are substantial and well documented, the potential hazards demand that exact criteria be established in selecting patients for the operation.

In the light of the experience cited in this paper, the young splenectomized patient requires close supervision for several years postoperatively so that immediate and energetic treatment may be instituted in the event of sudden and severe illness.

Specific prophylaxis presents manifold problems which await further study.

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ADDENDUM

Since the preparation of this paper, three similar cases have come to our attention. Two reported by Hoefnagel. (The Clinical Proceedings of the Children's Hospital, Washington, D. C., 12: 48, 1956) were brothers who had a splenectomy for thrombocytopenic purpura at four and six years of age, respectively. Seven months after splenectomy the younger child was admitted comatose with a temperature of 107.6°. Death ensued six hours later. Platelets were found to be deficient and postmortem examination revealed generalized hemorrhage including the adrenals. The other boy had three episodes of infection seven months, one year, and two years and nine months after splenectomy. These were associated respectively with (1) meningitis due to alpha hemolytic streptococcus, (2) a temperature of 106.6°F. and coma, and (3) the last illness with fever and convulsions to which he succumbed twelve hours after admission. Necropsy revealed evidence of generalized infection.

The third patient was observed by Dr. Janet Watson on the Pediatric Service of the King's County Hospital, Brooklyn, New York. The boy had a splenectomy at seven years of age for Cooley's anemia with excessive transfusion requirements. He was readmitted April 11, 1956, three years later, following the sudden onset of acute illness with a chill and a temperature of 106°F. Examination revealed a positive blood culture with pneumococcus type 33 but no source of the infection could be found. Prompt recovery ensued with penicillin therapy.

Of interest also are two recent papers which describe the occurrence of severe infection with congenital absence of the spleen. The first report, dealing with patients in the pediatric age group, mentions eleven cases including five of meningitis, in one of which there were no associated cardiac or other anomalies. (Ivemark, B. I., *Acta Paediat.*, Suppl. 104, 44: 65–67, 1955.) Another case, also without coexistent anomalies, (Myerson, R. M. and Koelle, W. A., *N. Eng. J. Med.*, 254: 1131, 1956) deals with an adult who suffered frequent infections with recurrent manifestations of the Waterhouse-Friderichsen syndrome.

The sixth case of acute benign pericarditis in this series occurred recently in a patient fourteen years of age with severe Cooley's anemia. Pericarditis with effusion, friction rub and characteristic electrocardiographic changes appeared four months after splenectomy (June 12, 1956).

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The Effect of Massive Prednisone and Prednisolone Therapy on Acute Leukemia and Malignant Lymphomas*

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ADRENAL cortical steroids have been extensively used in the management of the malignant lymphomas and leukemias. A reasonably predictable clinical and hematologic remission rate has been determined in acute leukemia of childhood following the administration of cortisone [*1*]. In the lymphomas and acute leukemia of adults, however, symptomatic improvement, temporary control of fever, bleeding and decrease in tumor masses has been noted only during the period of cortisone therapy; with discontinuation of the drug, prompt exacerbation of the signs and symptoms of the disease has usually occurred [*2*].

The present study was undertaken to ascertain the usefulness of "massive doses" of adrenocortical hormones (defined for the purposes of this study as 1 gm. daily of prednisone or prednisolone) in patients with acute leukemia and far advanced lymphomas. The minimal salt-retaining activity of prednisone† and prednisolone [*3*] made possible a dosage regimen which would have been very difficult or impractical to give with biologically comparable doses of cortisone, hydrocortisone or fluorohydrocortisone.

METHODS AND MATERIALS

Prednisone and prednisolone‡ were given orally in doses of 0.250 gm. every 6 hours to twenty-four patients with acute or subacute leukemia and ten patients with lymphomas. No difference in biologic or therapeutic effect was noted between prednisone and prednisolone and these compounds were therefore used interchangeably. Patients were given antacids and 3 gm. of potassium chloride daily. In most of the patients steroid therapy for this study was instituted at this high dosage level; five patients had received trials of 75 mg. daily of prednisone for a five- to ten-day period immediately prior to the institution of massive therapy, and four had received steroid in low dosage for varying periods earlier in their course. The total amount of prednisone used for the trial of "massive dosage" was generally about 12 gm. in the patients with leukemia; 10 gm. were given over a period of ten days and the dosage was then reduced to a maintenance dosage of 20 to 40 mg. daily or the drug was withdrawn completely. Three of the patients with acute leukemia, three patients in the acute myeloblastic stage of chronic myeloid leukemia, and eight of the patients with lymphomas had received a variety of agents prior to the institution of steroid therapy. (Tables I to III.)

† We wish to acknowledge with thanks the generous cooperation of Dr. Edward Henderson and the Schering Corporation for the supplies of meticorten® and meticortelone® which were used throughout this study.

‡ Early in the series cortisone in dosages up to 6 gm. daily was used in two patients.

RESULTS

Acute Leukemia. The criteria for the diagnosis, and for complete and partial remission in this disease were essentially the same as those employed by other investigators [*4*]. Thus for classification of complete remission, the peripheral blood, including hemoglobin, leukocyte count and platelet count returned to normal values, and the bone marrow showed less than 10 per cent blast forms. Three patients in whom findings were atypical are classified, somewhat arbitrarily, as having subacute leukemia. In two of these patients (P. L. and D. A.) the predominant abnormal cell was apparently of the "monocytic" or "myelomonocytic" group rather than a true blast. The third patient (E. W.) presented with a twelve-month history of anemia, and had a pancytopenia without

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TABLE 1

EFFECT OF PREDNISONE IN ACUTE LEUKEMIA

Patient	Age (yr.)	Sex	Diagnosis	Duration of Symptoms before Steroid Therapy	Previous Therapy	Effect	Comment	Current Status (after first course of massive steroid)
D. O.' B.	8	M	Acute leukemia	17 mo.	Cortisone, 6-MP	None	Died on 8th day of steroid therapy	Dead, 1 mo.
M. K.	28	F	Acute myeloid leukemia	3 mo.	Transfusions	Partial remission	Diabetes (transient)	Dead, 5 mo.
P. S.	58	M	Acute leukemia	12 mo.	None	None, (?) acceleration of disease	Hypomania	Dead, 1 mo.
R. K.	40	M	Acute leukemia	1 mo.	None	Complete remission	Subsequently 2 more complete remissions	Dead, 12 mo.
M. C.	33	F	Acute myeloid leukemia	3 mo.	Transfusions	None	.....	Dead, 1 mo.
I. M.	35	M	Acute leukemia	10 days	None	Complete remission	Subsequently 2 more complete remissions	Dead, 5 mo.
A. P.	42	F	Acute leukemia	5 mo.	6-MP, x-ray, transfusions, cortisone	None	.....	Dead, 1 mo.
J. C.	29	M	Acute leukemia ? monocytic	2½ mo.	Hydrocortisone	Partial remission	Infection, upper abdominal pain	Lost to follow-up, 2 mo.
L. Y.	26	F	Acute myeloid leukemia	3 mo.	Cortisone	None	Pregnant	Dead, 1 mo.
B. C.	70	M	Acute myeloid leukemia	3 wk.	None	None	.....	Dead, 1 mo.
S. R.	14	M	Acute lymphatic leukemia	2 mo.	None	Complete remission	Subsequently 2 more complete remissions	Living, 7 mo.
M. R.	27	F	Acute myeloid leukemia	1 mo.	Prednisone, 75 mg. daily	Partial remission	.....	Living, 5 mo.
M. F.	36	F	Acute myeloid leukemia	4 mo.	Prednisone, 75 mg. daily	Complete remission	.....	Living, 5 mo.
L. F.	69	F	Acute leukemia ? monocytic	5 mo.	Transfusions	None	.....	Dead, 1 mo.
N. diS.	32	M	Acute lymphatic leukemia	6 wk.	Prednisone, 75 mg. daily	Partial remission	.....	Dead, 2 mo.
A. Pa.	26	M	Acute lymphatic leukemia	2 wk	Prednisone, 75 mg. daily	Complete remission	.....	Living, 3 mo.
M. G.	33	F	Acute lymphatic leukemia	4 wk.	Transfusions, prednisone, 75 mg. daily	Partial remission	Pregnant	Living, 6 mo.
W F.	14	M	Acute myeloid leukemia	4 mo.	6-MP	Partial remission	.....	Living, lost to follow-up at 6 mo.

TABLE II

THE EFFECT OF PREDNISONE ON SUBACUTE LEUKEMIA AND THE BLASTIC CRISIS OF CHRONIC MYELOID LEUKEMIA

Patient	Sex	Age	Diagnosis	Duration of Symptoms	Previous Therapy	Effect	Current Status
P. L.	M	64	Subacute myelomonocytoid leukemia	3 mo.	None	None ? acceleration	Dead, 1 mo.
E. W.	M	64	Subacute leukemia, type unclassified	12 mo.	Transfusions	None ? acceleration	Dead, 1 mo.
D. A.	F	48	Subacute myelomonocytoid leukemia	3 mo.	None	Transient remission	Living, 8 mo.
A. P.	M	31	Acute myeloblastic stage of chronic myeloid leukemia	3 yr.	Radiotherapy	None	Dead, 1 mo.
W. D.	F	37	Acute myeloblastic stage of chronic myeloid leukemia	4 yr.	Myleran, x-ray	None	Dead, 1 mo.
M. T.	M	63	Acute myeloblastic stage of chronic myeloid leukemia	5 yr.	Myleran	Transient remission	Dead, 2 mo.

blast forms but with marked lymphocytosis in blood and bone marrow. These patients are listed in Table II which also includes three patients in the acute myeloblastic stage of previously diagnosed chronic myeloid leukemia. Symptomatic improvement, including decline in fever, improvement in appetite and in sense of well-being, occurred for at least a few days in most of the patients; symptomatic improvement was not classified as partial remission unless accompanied by improvement in the hematologic findings. The results are summarized in Tables I and II and may be conveniently broken down into four groups.

Complete remissions occurred in five of the eighteen patients with acute leukemia treated with massive doses of prednisone. Three of these patients (I. M., R. K. and M. F.) were over the age of thirty-five. Both patients I. M. and R. K. subsequently underwent relapse of the disease and in both, remissions were induced a second time with large doses of prednisone. Patient I. M. died five months after the onset of his disease; patient R. K. had three complete remissions (each two months or less in duration) but died with septicemia one year after the first appearance of symptoms. Patient S. R. relapsed four months after his first steroid-induced remission and has had a subsequent complete remission on the same therapy. Patient M. F. is still in remission five months after her first course of treatment. Patient A. Pa. had a complete remission on a regimen of massive prednisone after significant but incomplete improvement with 75 mg. daily over a period of two weeks. The remission was brief; relapse occurred within a month, at which time partial remission was induced with prednisone, 50 mg. daily.

Partial remission with definite hematologic improvement occurred in six of the eighteen patients with acute leukemia who had been treated. However, whereas the complete remissions were clearly related to the administration of steroid, it is difficult to relate some of the partial remissions so definitely to the administration of the drug. Indeed, in three cases partial hematologic remission followed cessation of the steroid and was accompanied by malaise and fever. These clinical symptoms responded to doses of 20 to 40 mg. daily of prednisone. Thus in patient M. K. partial remission manifested by disappearance of blasts from the peripheral smear, with bone marrow change from myeloblastic to myelocytic predominance, was first observed two weeks following the completion of steroid therapy. The evident hematologic improvement was accompanied by the appearance of fever with bilateral breast infiltrates; both the fever and the breast infiltrates responded to prednisone in a dosage of 50 mg. daily. In this patient hematologic and clinical relapse two months later were not affected by massive doses of prednisone and the patient died six months after the original diagnosis of acute myeloid

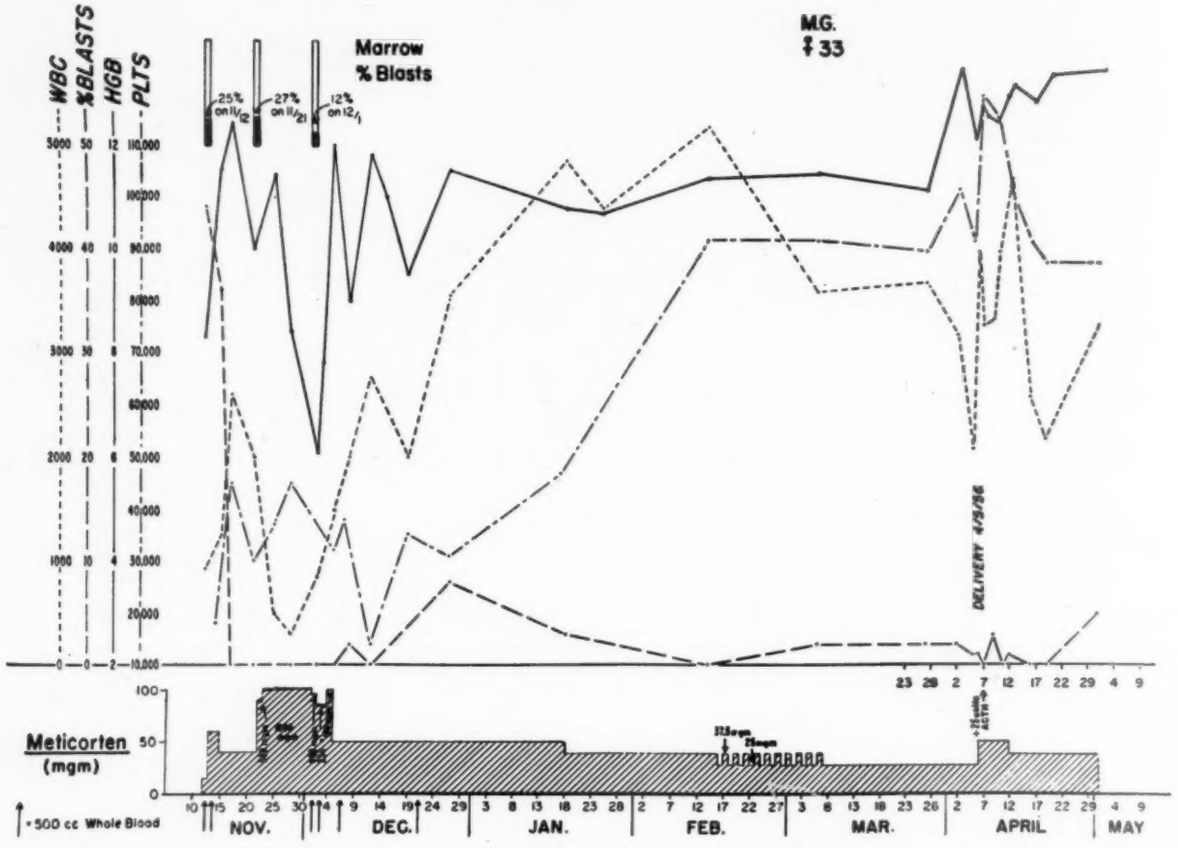

FIG. 1. Course of patient M. G. in whom the diagnosis of acute leukemia was made during pregnancy. The remission is classified as partial because of the failure of platelets to reach entirely normal levels and because the percentage of blasts in the bone marrow was not demonstrated to be lower than 12 per cent (see text).

leukemia had been made. In this case the relationship between the therapy and improvement, and the dissociation between the clinical and hematologic improvement make the evaluation difficult.

Patient M. R. had a similar hematologic improvement with massive prednisone therapy, although fever developed five days after withdrawal of the steroid. The fever was controlled by prednisone in a dosage of 30 mg. daily.

A partial remission was obtained in patient M. G., a thirty-three year old woman with acute leukemia, who developed purpura during the fourth month of pregnancy. Although she had a very good hematologic response to massive steroid dosage and delivered a living child, her remission is classified as partial because her platelet count never rose to normal levels and her marrow contained 12 per cent blasts on the last examination. The course of this patient is outlined in Figure 1.

In patient N. diS. a partial remission of brief duration occurred after the administration of massive doses of prednisone. This patient, a thirty-two year old man with diabetes, had had a complete remission three months previously on a daily regimen of prednisone, 75 mg. Thus while in patients N. diS. and M. G. partial remissions were clearly associated with the administration of prednisone, in three patients (M. K., M. R. and W. F.) partial remissions with hematologic improvement occurred after withdrawal of the massive doses of steroid; fever which appeared despite the hematologic improvement responded to small doses of the medication. This sequence of events is difficult to understand, and the significance of these partial late remissions remains obscure.

Even more difficult to evaluate is the remission obtained in patient J. C., a twenty-nine year old Puerto Rican man in whom the diagnosis of acute leukemia was made two and one-half months before steroid therapy was begun. This patient, on the fifth day of steroid therapy, had a

rise in white blood count from 31,000 to 164,000 per cu. mm., with 34 per cent early forms. Abdominal pain, nausea, fever and chills then developed and a blood culture was positive for Aerobacter aerogenes. The steroid therapy was withdrawn, and on a regimen of antibiotics he continued febrile for three and one-half weeks and received several transfusions. However during this three-week period his leukocyte count fell from a high of 164,000 to 1,400 per cu. mm. Because of the continuing fever and anemia, prednisone in doses of 40 mg. per day was instituted. The patient became afebrile promptly, the blasts declined to 1 per cent in the peripheral blood and the bone marrow showed considerable improvement. Whether this remission is related to the steroid therapy or is a remission following an acute superimposed illness, probably a penetrating ulcer, cannot be determined. Thus whereas the partial remission in patient M. K. is probably related to steroid therapy, the complicated course of events in patient J. C. precludes interpretation.

No benefit was noted in seven of the eighteen patients observed. These included an eight year old boy (D. O'B.) with acute myeloblastic leukemia of seventeen months' duration in whom the disease had become refractory to conventional doses of cortisone, 6-mercaptopurine and methotrexate before the large doses of steroid were tried. In patient L. Y. symptoms and hematologic findings of acute leukemia had developed during pregnancy; she had received cortisone (75 mg. daily) for four months prior to the administration of massive doses of prednisone. No effect of the prednisone, in either high or low dosage level, on the leukemic state was noted. The patient went into premature labor and delivered a stillborn baby. She died during the postpartum period and autopsy revealed, in addition to the findings of acute leukemia, a perforated peptic ulcer.

Possible acceleration of the leukemic process by massive doses of prednisone was noted in only one of the cases of acute leukemia. Many of the group who were classified as receiving no benefit were gravely ill and no accelerating effect could have been evaluated. However, patient P. S. had had symptoms of the disease for one year with no treatment before large doses of prednisone were given. His condition deteriorated rapidly while receiving massive steroid therapy and he died during withdrawal of prednisone. Since the disease had been present for a year, it is difficult to be sure that the accelerated downhill course was related to steroid therapy.

Subacute Leukemia. Partial remission. In the group classified as subacute leukemia, patient D. A. had a transient remission in association with the administration of massive doses of prednisone. This patient, a forty-eight year old housewife, showed decline in fever, regression of an enlarged cervical node, and definite improvement in both the peripheral blood and bone marrow picture; however complete remission was never obtained and her symptoms recurred promptly coincident with reduction in the amount of steroid. Her course was that of a partial remission; subsequently the patient has had buccal and cervical node infiltration with the appearance of many monocytoid cells in the peripheral blood. She has had another partial remission associated with the administration of 40 mg. daily of prednisone over a longer period of time.

No benefit and possible acceleration of the disease process was noted in two patients with subacute leukemia. Patient E. W., a sixty-four year old man, had had subacute leukemia and symptoms of anemia for about one year, without fever or severe hemorrhagic manifestations. He received "massive therapy" for ten days, and fever and ecchymoses developed for the first time during steroid withdrawal. The patient died thirty-six hours after the development of the fever. Aerobacter aerogenes was present in blood culture. Patient P. L., a sixty-four year old man, had fever for two and one-half months before the diagnosis of myelomonocytoid leukemia was made. Eight days after the institution of massive prednisone therapy he had a rise in leukocyte count (from 24,900 to 73,000 per cu. mm.). His hemoglobin dropped from 11 gm. to 6.4 gm. per cent with the appearance of icterus and reticulocytosis of 17 per cent. The cause of this hemolytic episode, which appeared during the course of prednisone therapy, was never ascertained; the patient died eleven days after the institution of prednisone. Permission for autopsy was not obtained. The course had been stable and rather slow prior to the institution of massive steroid therapy, and the accelerated downhill course with leukocytosis and a hemolytic crisis appeared suddenly; its relationship to steroid therapy is of course not proved. Indeed, in none of these cases can adverse effects of massive steroid therapy be proved. However since some authors have suggested that steroid therapy may

TABLE III
EFFECT OF PREDNISONE ON LYMPHOSARCOMA

Patient	Age	Sex	Diagnosis	Duration of Disease before Therapy	Previous Therapy	Effect of Prednisone Objective	Status
T. O'C.	53	M	Lymphocytic lymphosarcoma	2 yr.	X-ray, fair; CB1348, poor	Soft tissue mass regression	Dead, 3 wk.
E. B.	37	M	Chronic lymphatic leukemia	2½ yr.	X-ray, fair	WBC from 536,000 to 90,400, but no improvement in platelets	Dead, 1 mo.
L. P.	48	M	Reticulum cell lymphosarcoma	3 mo.	None	Improvement in hypercalcemia, clearing of psychosis	Dead, 3 mo.
G. P.	43	M	Reticulum cell lymphosarcoma	2 yr.	TEM, 6-MP, P^{32}, x-ray, HN_2, all fair	Marked improvement in skin lesions	Remission for 3 mo., received electron beam therapy 8 mo. after steroid and died 2 mo. later
A. R.	65	F	Reticulum cell lymphosarcoma	1 yr.	Thio-tepa, good	Marked reduction of lymph nodes and abdominal mass	Dead, 3 mo.
H. S.	47	F	Reticulum cell lymphosarcoma	1 yr.	X-ray, poor	Marked decrease in splenomegaly, improvement in hemogram	Living, 1 yr.
C. F.	57	M	Reticulum cell lymphosarcoma	2 yr.	X-ray, good	Decrease in enlarged lymph nodes, parotid and liver.	Dead, 6 wk.
J. F.	59	F	Reticulum cell lymphosarcoma	3 yr.	X-ray, good	Tumors increased in size	Dead, 2 mo.
S. G.	32	M	Reticulum cell lymphosarcoma and acute leukemia	5 mo.	None	Improvement in superior mediastinal compression and in peripheral blood counts	Dead, 1 mo.
E. P.	33	M	Reticulum cell, lymphocytic lymphosarcoma, acute leukemia	2 yr.	X-ray, good	Decrease in liver and spleen, control of purpura	Dead, 2 mo.

accelerate the course of myelogenous leukemia, attention is drawn to the possibility in these cases [*1*].

No significant benefit was obtained from massive prednisone therapy in three patients in the terminal blastic phase of chronic myeloid leukemia, although one patient had transient hematologic improvement.

Lymphomas. Massive steroid therapy was employed in a small group of patients with lymphosarcoma and one patient in the terminal phase of chronic lymphatic leukemia. In a group of more than twenty patients with Hodgkin's disease and lymphosarcoma, prednisone was used in daily doses up to 500 mg. This latter series will be discussed in general rather than in detail since there was no essential difference in the tumor response with prednisone than has been observed with other adrenal cortical steroids.

Table III summarizes the experience with daily doses of 1 gm. of prednisone in the lymphomatous diseases. Eight of the ten patients had disseminated reticulum cell lymphosarcoma which is notably more refractory to radio- or chemotherapy than the related lymphocytic or giant follicular lymphosarcoma. With a single exception (J. F.) there was an impressive objective effect of the prednisone on the tumors, accompanied in every instance by subjective

improvement. Unfortunately, again with only a single exception (H. S.), the objective and subjective improvement persisted only as long as the therapy was given. When the dosage was reduced to 100 mg. daily or less, signs and symptoms began to recur. Inasmuch as prednisone in massive doses has significant toxicity, the drug could not be maintained without hazard. The brevity of the improvement, when it occurred, is emphasized by the outcome in these patients with reticulum cell lymphosarcoma. Only one patient is still living one year after steroid therapy had been initiated. It is noteworthy that this patient had hypersplenism (manifested by splenomegaly and pancytopenia) associated with the tumor. Six of the seven remaining patients were dead in three months or less after the onset of prednisone treatment. No significant benefit was achieved in one patient in the terminal phase of chronic lymphatic leukemia.

Side Effects of Massive Steroid Therapy. The large doses of prednisone employed in this study frequently produced, within ten days, many of the side effects usually seen with more prolonged courses of therapy. Rounded facies developed in all the patients before the ten-day course was completed. Complaints of intense hunger and increase in nervous tension were common. Objective hyperactivity proceeding to hypomania developed in one patient.

In two patients glycosuria with elevated blood sugars was demonstrated; however with this short course of steroid therapy the management of diabetes was a problem only in a third patient (N. diS.) who was known to have diabetes prior to the administration of steroid. In patients receiving doses of prednisone up to 500 mg. daily for the symptomatic control of Hodgkin's disease and other lymphomas, the drug was necessarily continued for weeks. In three of these patients diabetes constituted a major problem, complicated by diabetic acidosis in two.

The development of severe hypertension did not occur in the patients under study. This was not unexpected since the patients were in a younger age group for the most part. Salt and water retention is known to occur with the large doses of prednisone used but this was observed in only four of the thirty-four patients studied. Muscular weakness secondary to hypokalemia occurred once.

Peptic ulceration constituted a particularly serious hazard of the administration of massive doses of prednisone. Of the group with leukemia one patient had a perforated duodenal ulcer at necropsy and two others showed signs and symptoms of a penetrating ulcer within eight days after the institution of prednisone. In two patients receiving doses of 500 mg. prednisone

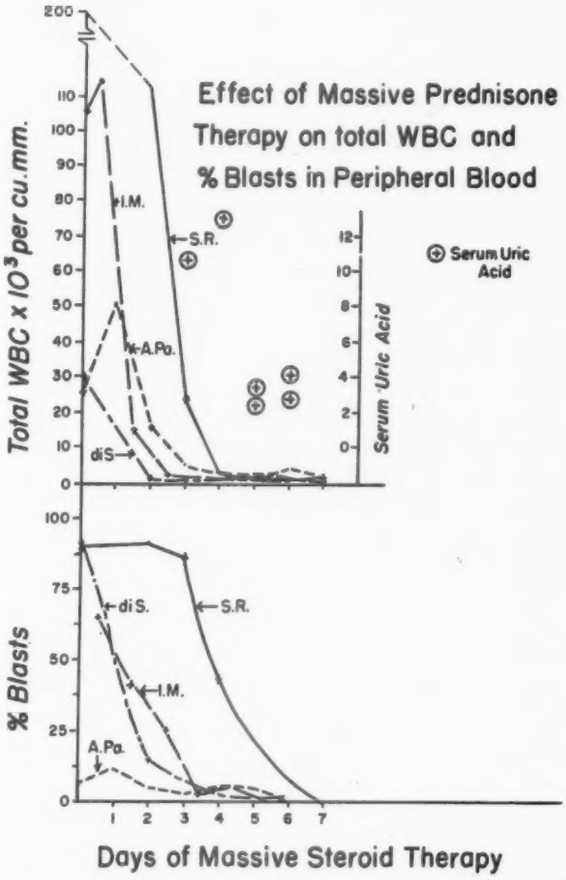

FIG. 2. The leukocyte counts and percentage of blasts in peripheral blood of four patients with leukocytosis who had marked decreases in leukocyte counts on massive prednisone therapy.

daily for Hodgkin's disease signs of a perforated viscus developed within two weeks of the institution of therapy. In all instances the manifestations of gastrointestinal ulceration appeared while the patients were maintained on an "antiulcer" regimen.

Finally, infection was an important and grave complication of the massive steroid therapy. Bacteremia, septicemia and local pyogenic infections were observed in one-third of the cases. One instance of generalized cryptococcosis was found in a patient with lymphosarcoma. These infections were not readily controlled with antibiotics, perhaps because of the frequent associa-

tion of leukopenia and perhaps also because of the depression of antibody formation by the steroids.

Attention should be drawn to the rapid decline in peripheral leukocyte count which is occasionally seen within a few days after the initiation of steroid therapy. Examples of this are to be found in Figure 2. The extreme rapidity of this phenomenon is illustrated by patients I. M. and S. R. in whom total leukocyte counts of over 100,000 and 200,000, respectively, had declined to leukopenic values in four days. The rapidity of this reaction suggests leukocyte destruction or segregation from the peripheral blood; however, we have repeatedly observed in these patients a concomitant hypocellular marrow at the time of leukopenia. A possible alternative explanation for the hypocellularity of the bone marrow might be arrest of polymorphonuclear neutrophil formation. An important consideration with this rapid drop in leukocyte count is the frequent increase in serum and urinary uric acid and the associated urinary suppression. We have not encountered urinary suppression; however, as a precaution patients with leukocytosis have been on a high fluid intake throughout the course of steroid therapy. While some of the patients have had hyperuricemia before and during treatment, in others normal or low uric acid values have been found in association with this rapid decline in leukocyte count.

COMMENTS

Massive dosages of adrenal steroids have been given by Hill and Vincent [5] who used cortisone and prednisone in conjunction with antimetabolite drugs for acute leukemia. In the present study adrenal steroid therapy was not combined with other drugs since an attempt was made to evaluate the efficacy and toxicity of this form of therapy alone.

Since complete remissions occurred in five of eighteen patients with acute leukemia treated with large doses of adrenal steroids, a preliminary evaluation of the usefulness and toxicity of this form of therapy is desirable, although complete evaluation is not possible at this time. The appearance of considerable toxicity, with peptic ulcer, bacteremia, psychoses and intensification of diabetes with attendant acidosis makes an evaluation of the chances of benefit for a particular patient even more desirable. Although the total experience is small, the use of these massive steroid dosages in "subacute" leukemia, or in the "acute blastic crisis" of chronic myeloid leukemia, did not seem to be worthwhile.

The level of leukocyte count did not seem to be an important factor in obtaining remissions since complete remissions were noted in patients with high or normal total leukocyte counts.

Unfortunately, it was frequently not possible to establish the variety of acute leukemia which was being treated; the morphologic classification of acute leukemia is often difficult, and occasionally the distinction between acute lymphatic and acute myelocytic leukemia cannot be made with certainty. Therefore no general conclusions were drawn about the relationship of the variety of acute leukemia and the response to therapy; most, but not all, of the complete remissions occurred in patients in whom blood smears were perhaps more compatible with lymphocytic leukemia than with the myeloblastic variety.

Experience is insufficient to yield any definitive statement about the relationship of the age of the patient to response to therapy. The comparative refractoriness of acute leukemia of adults to all forms of therapy is well recognized. However three of the patients who remitted completely in this series were between thirty-five and forty-one years of age, and in this age group good responses to the antimetabolite compounds are uncommon. Since the results with other less toxic agents, notably 6-mercaptopurine, and lower doses of steroid are reasonably good in children, the use of these massive doses of steroid with their attendant toxicity is probably not justified in younger patients until other measures have failed.

In the present small series no effort was made to explore various dosage regimens. Although five of eighteen patients had complete remissions associated with massive prednisone therapy and six of the remainder had partial remissions, some of which were reasonably ascribed to the drug, we would be loath to recommend this as the treatment of choice for acute leukemia of adults. Our reservation rests on two facts: The duration of remissions is measured in periods of months and no patient has survived beyond one year; the complications of side effects of large doses of prednisone are serious, frequent and often difficult to combat. For these reasons it is our belief that a more reasonable procedure would be to employ doses of 100 mg. daily of prednisone or

prednisolone in adult acute leukemia. If there is only partial improvement, the amount of drug may be increased cautiously. If there is no effect, improvement from massive doses is too remote, the likelihood of forbidding toxicity is too great, and the significance of the benefit, even if obtained, is too little to warrant the trial.

This small series includes two patients (L. Y. and M. G.) who had their first manifestations of acute leukemia during pregnancy. One patient (L. Y.) received large doses of steroid during the eighth month of pregnancy when her condition was deteriorating rapidly. She delivered a stillborn baby and died in the postpartum period. The other patient (M. G.) (Fig. 1) had moderately severe hemorrhagic manifestations early in pregnancy. On massive prednisone therapy, followed by maintenance doses, she had a nearly complete hematologic remission with an uneventful pregnancy and premature delivery of a living baby.

The effect of large daily doses of prednisone on the course of the malignant lymphomas was studied in only a small group of patients. This trial was selective in that all of the patients either had had the limit of radiotherapy and chemotherapy or there were existing hematologic contraindictions to therapeutic modalities which might further depress hematopoiesis. The patients were further selected in that eight of the ten had reticulum cell lymphosarcoma, the type of lymphoma which is most refractory to any form of treatment now available. Recognizing that the trial of prednisone therapy was weighted against the drug, certain conclusions can be drawn from the experience. With the exception of patient H. S., no significant modification of the natural history of the disease was achieved. This patient, whose chief problems were related to the hypersplenism associated with the reticulum cell lymphosarcoma, has been returned to normal useful living. All of the others studied showed objective tumor regressions but these were transient and failed to change the course of their illness. Particularly impressive in this group of patients were the toxic side reactions of the massive steroid therapy. Seven of the ten patients had one or more of the major forms of toxicity discussed in preceding paragraphs. So forbidding are these manifestations that it is clear that massive steroid therapy can be justified only as a heroic measure to meet a desperate situation, and then administration must be limited to a relatively brief period of time. On the basis of our experience, the lymphomas do not appear to fall into this group.

SUMMARY

1. The administration of large doses of prednisone or prednisolone in eighteen cases of acute leukemia resulted in clear-cut complete remissions in five cases and partial remissions in six. Two of the partial remissions were not clearly related to administration of the steroid. The complete remissions occurred in adults whose ages were forty, thirty-six, thirty-five, twenty-six and fourteen.

2. In one patient with a subacute myelomonocytoid leukemia a brief and transient remission was obtained.

3. In three cases, including two of atypical or subacute leukemia, and one of acute leukemia there might have been some acceleration of the disease process by the administration of steroid. However in all these cases alternative possibilities in terms of infection or gastrointestinal perforation might have explained the accelerated downhill course.

4. Although objective remissions were produced by steroid administration in most of the ten patients with malignant lymphomas, the course of the disease was not significantly modified and side reactions were serious.

5. Complications of therapy included the development of diabetes, bacteremia, septicemia, local pyogenic infection and generalized fungus infection, psychoses, gastrointestinal ulceration and perforation.

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Studies on Serum Aldolase Activity in Neuromuscular Disorders*

I. Clinical Applications

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In most instances of neuromuscular disease a diagnosis can be established with assurance on the basis of clinical appearance and evolution of the disorder. The need for laboratory assistance arises, however, in the incipient or obscure cases which are characterized by progressive weakness, skeletal muscle atrophy, and clinical features which may be jointly shared by several neuromuscular disease entities. Of the various laboratory adjuncts currently available, roentgenographic examination may assist in quantitating the degree of muscle wasting and even in charting its regional distribution, but cannot determine the intrinsic nature of the muscle process [*1*]. The creatine-creatinine ratio serves to indicate some aspects of muscle metabolism but its lack of specificity renders it of little diagnostic value [*2*]. Muscle biopsy still remains the most reliable diagnostic help in delineating such disorders as progressive muscular dystrophy. The procedure, however, usually requires hospitalization. A simple serologic test indicating the nature of skeletal muscle atrophy would be of help in distinguishing some of these occasionally confusing primary or secondary muscle diseases.

Recently a group of French observers reported that some constituents of muscle, particularly the glycolytic enzyme fructoaldolase, may be elevated in serums derived from patients with some diseases involving muscle [*3,4*]. The present study was undertaken to determine the significance of the serum aldolase concentration in a wide variety of primary and secondary neuromuscular disorders. An attempt was also made to compare these data with the results obtained by a study of some other enzymes involved in muscle metabolism. Wherever feasible, histologic examination of biopsied muscle tissue was performed for independent confirmation of the clinical diagnosis. Occasional biopsies were made to determine also the tissue levels of aldolase and phosphorylase.

MATERIAL

Because of the heterogeneity of neurologic diagnoses comprising the 238 patients of the present study, the various anatomic components of the neuromuscular system involved in the underlying disease process were used as the criteria for division into six categories. Additional note was made of the time interval between the onset of clinical illness and the time that the serum aldolase levels were determined. In all instances muscular atrophy, paralysis and/or involuntary movements were evident.

Progressive Primary Myopathies. This group included thirty-seven patients with progressive muscular dystrophy, ranging in age from four to fifty-four years. In the majority of cases the diagnosis was previously established by protracted clinical observation and muscle biopsy. Three cases of myotonia dystrophica were also assigned to this category.

Progressive Nuclear Myelopathies. Conditions characterized by continuing spinal cord anterior horn cell degeneration were assigned to this group, acknowledging the fact that in certain of these ailments other morphologic changes were present. The affection of the lower motor neuron was believed, however, to be the predominant physiologic disorder referable to the integrity of skeletal muscle. Thus, for example, amyotrophic lateral sclerosis was included in this group despite an associated upper motor neuron defect. Similarly, Tay-Sachs' disease was included because of the progressive degeneration of the anterior

* From the Isaac Albert Research Institute of The Jewish Chronic Disease Hospital, and the Departments of Pathology of The State University of New York, College of Medicine, and The Albert Einstein College of Medicine, New York, N. Y. Supported by a grant from The National Foundation For Muscular Dystrophy, Inc.

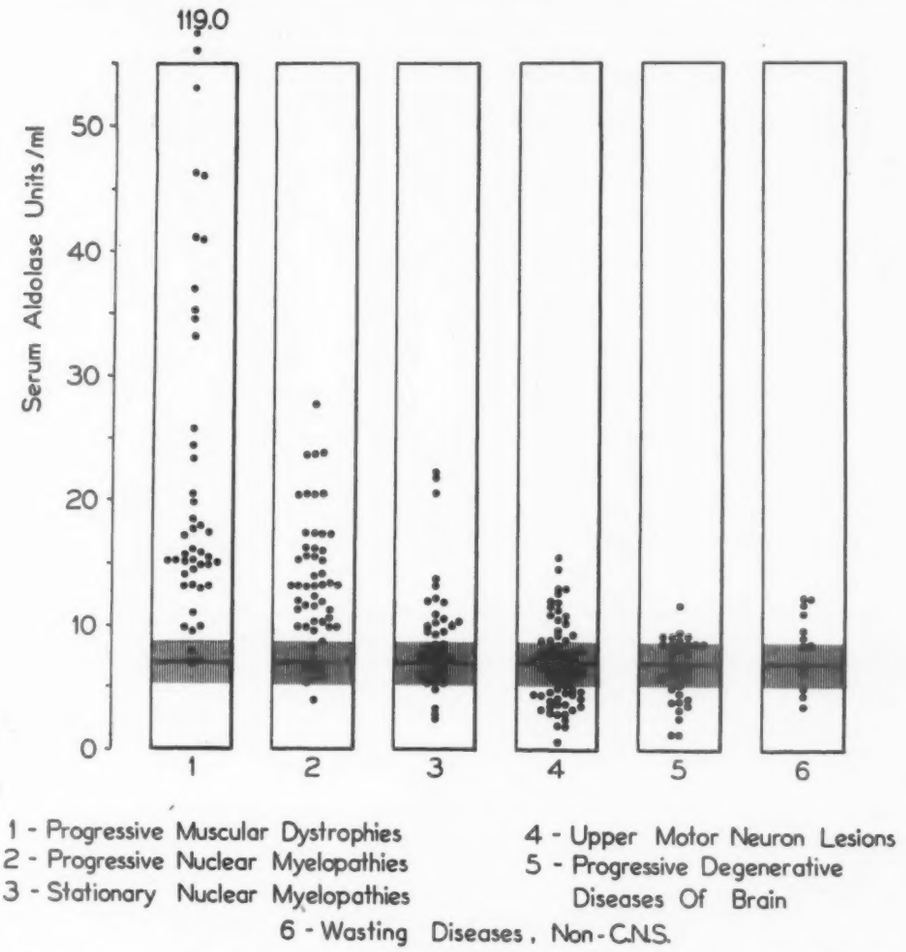

FIG. 1. Serum aldolase concentration in 238 patients with muscular and neuromuscular disease.

horn cells of the entire spinal cord. Other diseases in this division included amyotonia congenita, progressive spinal muscular atrophy and arthrogryposis multiplex congenita. This latter illness has been considered to be fundamentally a degenerative disease of anterior horn cells [*5,6*].

Stationary Nuclear Myelopathies. This category encompassed diseases of the spinal cord, principally affecting anterior horn cells, in which progression was not prominent. Thirty-eight cases of convalescent or remote poliomyelitis were included on the assumption that the anterior horn cell necrobiosis was terminated within days after the onset of the illness and that no further neuronal destruction developed in the ensuing months in spite of continuing muscle atrophy. The shortest time interval between onset of paralysis and serum aldolase determination was four months, the longest, fifteen years. Seven instances of meningomyelocele and three cases of paraplegia attributable to compressive neoplasm or granulomatous lesion were incorporated into this group, recognizing that an extensive corticospinal tract deficit coexisted with the segmental anterior gray matter disability.

Pyramidal Tract Diseases. Functional severance of the upper motor neuron system to the exclusion of any ventral horn cell disorder was established as the standard for inclusion in this category. Forty cases of vascular encephalomalacia, with variably severe limb paralysis, were studied. In the majority of cases the vascular occlusion was incurred years before application of the aldolase test. It was thus assumed that extensive pyramidal tract degeneration had developed and that any effect upon serum aldolase level would be fully apparent at the time of enzyme determination. In most instances the paralytic residua were marked enough to necessitate permanent institutionalization.

Diffuse Degenerative Central Nervous System Diseases. Multiple sclerosis, Schilder's disease, cerebral palsy, Parkinsonism, basal ganglionic disorders of undetermined type, dystonia musculorum deformans and hereditary ataxia, a total of sixty-nine cases, were assigned to this category. In many instances an overlapping with other groups was unavoidable. Pyrami-

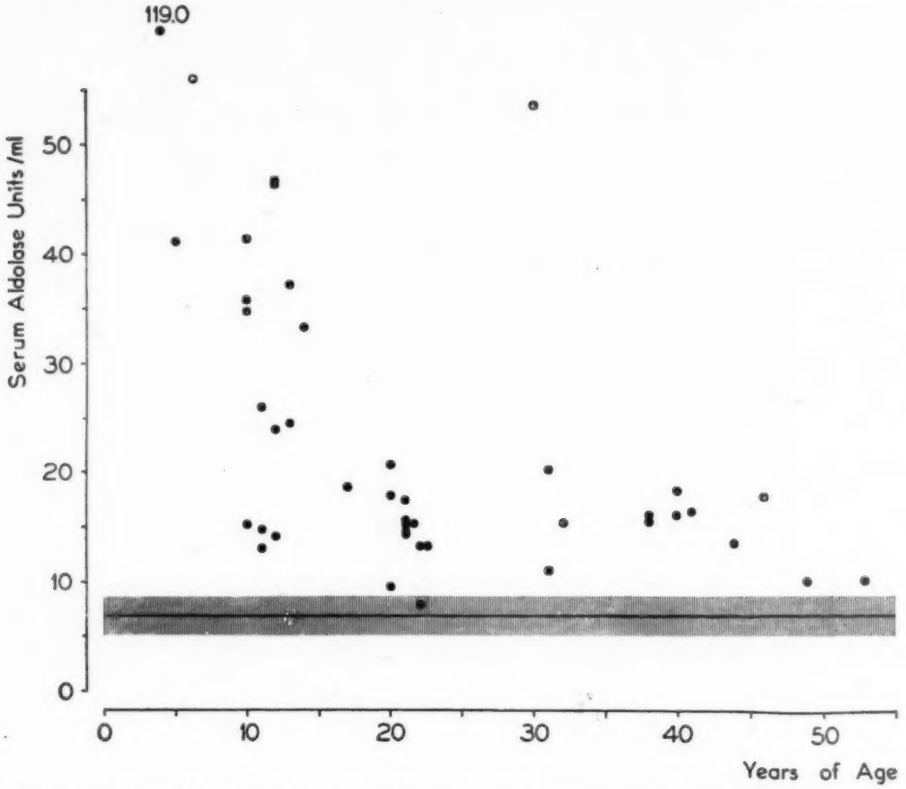

FIG. 2. Relationship of age to serum aldolase in thirty-seven cases of progressive muscular dystrophy.

dal tract degradation was a conspicuous finding in many such cases but cerebral hemisphere disease was paramount.

Muscular Atrophy of Non-neurologic Origin. Twenty-nine cases of severe and incapacitating illness, mainly rheumatoid arthritis, were included because of the extensive muscle atrophy. Clinical examination indicated that the nervous system played no role in the muscular wasting.

METHODS

The serum and tissue aldolase determinations were carried out according to the method of Sibley and Lehninger [7]. Muscle phosphorylase was determined by the technic of Cori et al. [8]. The SGO-transaminase levels were performed according to the procedure described by Karmen, Wroblewski and La Due [9].

RESULTS

Serum Enzyme Activity. (Fig. 1.) Normal serum aldolase levels were established on the basis of determinations in fifty healthy, ambulatory individuals of varying age and thirty patients with non-debilitating illnesses. No significant variation due to age, sex or temporary illness was noted. A normal value of 7.14 ± 0.73 units/ml. was established in this laboratory, in essential conformity with normal levels determined elsewhere [10].

Progressive primary myopathies: A significant increase in serum aldolase levels was recorded in thirty-two of the thirty-seven patients with muscular dystrophy studied in this series. (Table 1.) The over-all average of serum aldolase was 23.88 units/ml. with a range varying from 7.2 to 119.0 units. There was little correlation between the height of the serum enzyme and the clinically evaluated severity of the disease. Normal values were generally obtained in patients in whom the disease process was quiescent during and for the years preceding the aldolase determination. A definite relationship was apparent between the level of serum enzyme activity and the age of the dystrophic patients. Eight children afflicted with the disease displayed extremely elevated levels. Thus when plotted graphically, an inverse correspondence between age and increase of serum aldolase was clearly noticeable. (Fig. 2.) In a few cases of the childhood form of pseudohypertrophic muscular dystrophy the opportunity for monthly serial determinations was available. A

TABLE 1
SERUM ALDOLASE CONCENTRATION IN 238 PATIENTS WITH MUSCULAR ATROPHY

Category	No. of Patients	No. of Determinations	Serum Aldolase Units
Primary myopathies	37	53	23.88*
Muscular dystrophy (ages 4–14)	10	17	43.33 ± 7.0
Muscular dystrophy (ages 15–34)	14	23	15.73 ± 1.8
Muscular dystrophy (ages 35–70)	10	10	11.56 ± 1.2
Myotonic dystrophy	3	3	6.80
Progressive nuclear myelopathies	15	55	12.74
Amyotonia congenita, arthrogryposis, amyotrophic lateral sclerosis	7	22	10.17 ± 0.9
Tay-Sachs' disease	8	33	14.46 ± 0.9
Stationary nuclear myelopathies	48	77	8.82
Post-poliomyelitis	38	60	9.04 ± 0.5
Compressive myelopathies	10	17	8.00 ± 0.8
Pyramidal tract disease	40	67	6.21 ± 0.4
Diffuse degenerative central nervous system diseases	69	117	8.04
Multiple sclerosis	14	23	6.09 ± 0.7
Cerebral palsy	16	37	9.47 ± 0.5
Parkinsonism	6	7	6.20 ± 1.0
Miscellaneous†	33	50	8.14 ± 0.5
Muscular atrophy non-neurologic	29	40	6.98 ± 0.5
Normal	80	80	7.14 ± 0.73

* Mean for the entire group.
† See text.

gradual fall in the serum level of the enzyme was noted. (Fig. 3.) There was no correlation between clinical forms of the disease (e.g., facioscapulo-humeral) and serum aldolase level. The average for males with muscular dystrophy was distinctly higher than for females, but this discrepancy was undoubtedly caused by the fact that all eight children in the series were boys, a sex-linkage commonly recognized in the childhood form of the disease [*11*]. In three patients with myotonia dystrophica, all adults, normal values were noted.

Progressive nuclear myelopathies: Results in this category disclosed uniform elevation of the serum aldolase but never to the degree found in patients with muscular dystrophy of comparable age. The average for the entire group of fifteen cases was 12.74 units/ml. Variations between the diseases comprising this division were noted. (Fig. 4.) The aldolase values obtained in the seven patients with Tay-Sachs' disease were uniformly higher than levels noted for amyotonia congenita or amyotrophic lateral sclerosis. The number of cases of ventral horn cell abiotrophy was considered too small to reach any conclusions concerning relationship of severity,

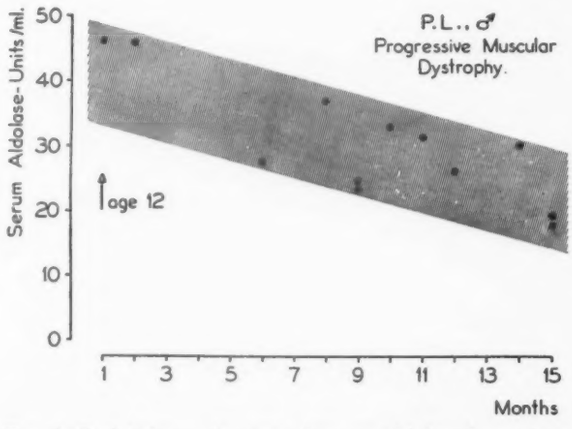

FIG. 3. Serial determination of serum aldolase in patient P. L., a young male with progressive muscular dystrophy.

age, duration of disease and serum aldolase value.

Stationary nuclear myelopathies: Compiled findings showed a minimal elevation in some cases of convalescent poliomyelitis. No rise in serum aldolase was recorded in the children with meningomyelocele or the adults with compressive or traumatic paraplegia. The elevations in the post-poliomyelitis group were of limited

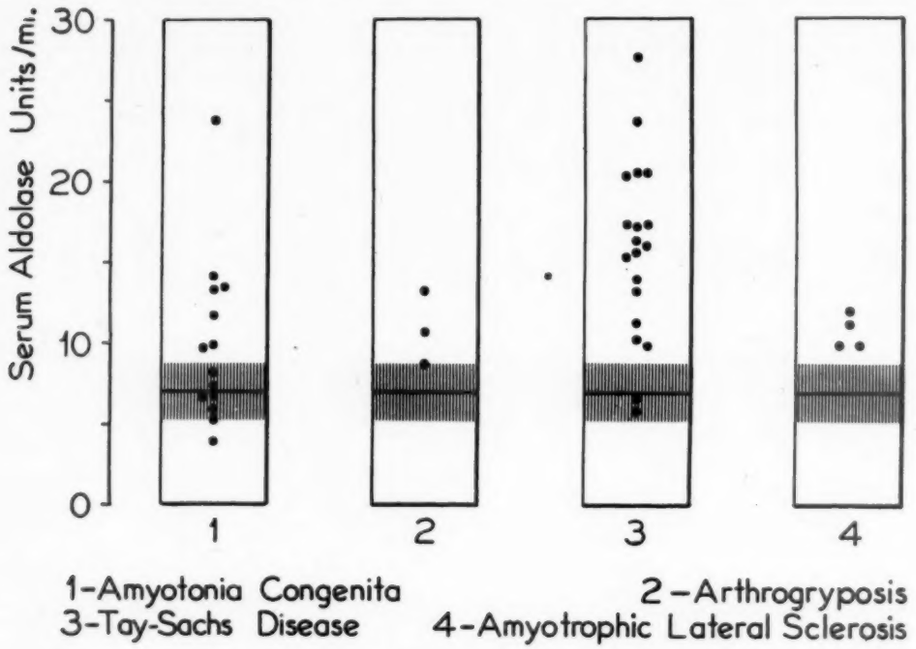

FIG. 4. Serum aldolase concentration in cases of progressive nuclear myelopathies.

magnitude and with the exception of one child, never exceeded 14 units/ml. In patients who had poliomyelitis in the distant past, serum aldolase levels were either normal or below normal.

TABLE II
MEAN BIOCHEMICAL CHANGES IN MUSCLE TISSUES IN THREE CASES OF PROGRESSIVE MUSCULAR DYSTROPHY

	Non-collagenous Protein* (%)	Phosphorylase† A	Phosphorylase† B	Aldolase†
Normal	13.8	9,426	21,197	26.2×10^4
Muscular dystrophy	9.4	4,180	11,050	1.8×10^4

* Calculated as percentage of the total wet weight of muscle tissue sample.
† Calculated in units of enzyme present per gram of non-collagenous protein.

Pyramidal tract diseases: The composite average of the entire group of forty patients in this division was well within normal limits. In two cases levels were above the assigned upper limits of normal. On subsequent determination of the serum aldolase, however, the results reverted to normal.

Diffuse degenerative central nervous system diseases: Serum aldolase values in the sixty-nine patients in this category were essentially within normal limits. In many patients with protracted disease, such as multiple sclerosis, the serum aldolase was depressed below normal.

Muscular atrophy of non-neurologic origin: Normal values were almost uniformly obtained. An occasional value was slightly above normal but succeeding evaluation showed invariable recession to normal. No clinical explanation for these rare fluctuations was forthcoming.

Further Enzyme Studies. Portions of fresh tissue obtained at the time of diagnostic muscle biopsy were occasionally utilized for determination of tissue levels of aldolase as well as phosphorylase. A striking depression of enzyme activity was seen in the muscular dystrophy cases even when the enzyme, aldolase or phosphorylase, was equated against the non-collagen nitrogen content rather than the wet tissue weight. (Table II.) This latter calculation precluded any invalid interpretation which did not take into account the probability of extensive fatty and fibrous tissue replacement. Normal values were ascertained in normal skeletal musculature resected during the course of surgical procedures on patients not afflicted with neurologic or muscular disease. A considerable fluctuation was seen in the phosphorylase content of normal muscle, possibly reflecting the extreme lability of this agent; the tissue level of phosphorylase in muscular dystrophy, however, fell below the range of normal variation recorded in this laboratory.

SGO-transaminase levels were obtained in representative patients derived from the categories listed. No consistent or significant elevations were observed in cases of muscular dystrophy or in the other illnesses studied.

COMMENTS

The serum aldolase technic has been suggested as a diagnostic aid in many unrelated diseases. Elevation of the serum enzyme level has been described in malignant neoplasms of animals [*12*] and man [*13*], primary myopathy [*3*], hepatic disease [*14*], patients with extensive tissue necrosis (e.g., gangrene, pancreatitis) [*10*] and alcoholic psychosis [*10*]. While the action of aldolase in the chain of intracellular glycolysis is highly specific, the enzyme is so ubiquitous that an isolated abnormal value is of little assistance unless appropriately viewed against the clinical background. It was in this context that the test was applied to 238 patients with neurologic and related disorders. Care was taken to exclude patients with visceral lesions capable of causing hyperaldolasemia. It was thought desirable to evaluate the procedure in a multiplicity of organic disorders exhibiting the common denominator of muscular atrophy. Classification of cases was dependent upon the site of the abnormality causing the atrophy and the presence of absence of continual activity rather than the magnitude of muscle wasting.

A pronounced rise in serum aldolase was apparent in most cases of muscular dystrophy, thus confirming the results of Schapira et al.[*4*]. An inverse relationship between age of the patient and enzyme level was evident, children below the age of eleven showing a notable elevation while adults were more prone to exhibit a modest rise in the serum level of the enzyme. The present data suggest that a serum aldolase level greater than 20 units in a child with muscular disorder is indicative of progressive muscular dystrophy.

These studies may be construed as confirming the impression of some that the childhood form of muscular dystrophy is fundamentally independent of the myopathic syndromes emerging in maturity. Indisputable differences do exist between the two forms of the disease: the topographic pattern of muscle involvement is often dissimilar, the facio-scapulo-humeral presentation more often associated with the adult variety; the genetic substrates differ, the childhood form being recessive; and the prognosis is certainly less grave in the adult type of muscular dystrophy. The histopathologic alterations, however, are similar and it is the opinion of others [*15*] that these two forms represent modifications of a basically indivisible disorder. Four of the younger patients with progressive muscular dystrophy were tested by this serologic procedure for periods up to fifteen months. While monthly fluctuations were recorded, a continuing decline of the hyperaldolasemia was always observed. Thus when serially studied, the reciprocal correlation between age and serum aldolase elevation was also noted in the same patient. The distinction between the childhood and adult forms of muscular dystrophy cannot, therefore, be further substantiated on the basis of this test.

An inverse relationship between serum and muscle enzyme level was also apparent. The hyperaldolasemia evident during the evolution of muscular dystrophy probably represents a release of intracellular aldolase, as postulated by others [*4*]. The rate of muscle degradation in muscular dystrophy lessens as the disease proceeds. This reflects itself in a lowering of the serum aldolase concentration as compared to the high serum enzyme activity representative of the early phases of the disease. The serum aldolase test cannot be interpreted as an indicator of the volume of muscle destroyed but rather as a function of muscle breakdown at the time of the test.

The serum aldolase concentration in patients with muscular atrophy attributable to lower motor neuron disease was surveyed because of occasional difficulties encountered in distinguishing this form of disease from the primary myopathies. Application by others has failed to indicate any indisputable serum aldolase abnormalities [*4,10*]. Patients with progressive spinal atrophy, amyotonia congenita and related diseases were tested by Schapira and his associates [*4*]. A slight rise in serum aldolase is evident from their compiled statistics but in the opinion of these authors the elevation was of no significance. They did comment, however, upon occasional moderate rises in instances of convalescent poliomyelitis.

In the presently reported series a statistically valid rise in aldolase was demonstrated in cases of progressive lower motor neuron disease (progressive nuclear myelopathies). Four patients with amyotonia congenita invariably showed levels above 10 units/ml., the upper limits of normal. In amyotrophic lateral sclero-

sis, a comparable disease of adulthood, high normal values were noted. In Tay-Sachs' disease the unequivocal elevation of serum aldolase was interpreted as indicating the extent of anterior horn cell involvement; however, since the neurocellular degeneration characteristic of Tay-Sachs' disease extends well beyond the motor elements of the central nervous system, the validity of this conclusion may be open to question. It is conceivable that the glycolytic enzyme is liberated directly from neural tissues undergoing destruction. Comparative studies with other diffuse nervous system disorders in which anterior horn cells were relatively preserved indicated no rise in the serum aldolase. Normal or subnormal values were obtained in instances of Schilder's disease, Friedreich's ataxia, multiple sclerosis and even in cases of encephalomalacia, in which indiscriminate necrobiosis is an acknowledged occurrence.

Thus in the entire range of neurologic diseases surveyed only those with anterior horn cell deficit exhibited a rise of serum aldolase. The magnitude of muscle atrophy bore no correspondence to the extent of hyperaldolasemia. Far greater muscle wasting was often evident in cases of cerebral degenerative disease or in patients suffering from incapacitating somatic illness with uniformly normal serum aldolase levels. These findings suggest that the muscle atrophy induced by deterioration of the lower motor neuron complex differs fundamentally from the atrophy due to incapacity or diffuse cerebral disease. The metabolic integrity of sarcoplasm is intimately dependent upon the axonal connections to the nervous system. Experimental neurotomy leads to profound changes in the lipid and electrolyte constituents of muscle [*16*]. A decrease in muscle aldolase and phosphorylase has been reported following nerve section [*17*], and confirmed in this laboratory [*18*].

The suggested mechanism for aldolase release in lower motor neuron disease would not apply to muscular dystrophy since the nervous system in this illness is considered unaffected. It is likely that the hyperaldolasemia of muscular dystrophy is not immediately related to any intrinsic metabolic disorder since a similar rise in serum enzyme level is noted in non-specific muscle necrosis. In myocardium, which contains a great amount of this enzyme, a relatively small area of infarction produces a dramatic but evanescent rise in the serum aldolase levels. This procedure has been used as a diagnostic test in acute myocardial infarction of humans and has been corroborated in experimental animals [*19*]. The hyperaldolasemia in such cases is similar to the transient but marked rise in SGO-transaminase seen in patients suffering from acute coronary artery occlusion [*20*]. The SGO-transaminase test was applied to selected cases of muscular dystrophy. Only occasional elevations were forthcoming, indicating that these two enzymes may not necessarily show parallel alterations in the many diseases in which each has been applied.

SUMMARY

The serum concentration of the glycolytic enzyme, fructoaldolase, was determined in 238 patients with muscular and neurologic disease.

A pronounced elevation of this enzyme was found in cases of progressive muscular dystrophy, coupled with a depression of aldolase within the affected musculature. The highest serum values were recorded in the childhood form of the disease. A continuing decrease in the hyperaldolasemia was linked with progressive duration of the disease.

A minimal rise in serum aldolase was apparent in young patients with degenerative anterior horn cell disease (e.g., amyotonia congenita).

Normal or subnormal serum aldolase values were obtained in cases of diffuse vascular or degenerative cerebral disorders in spite of extensive muscle atrophy. Similarly, severe muscle wasting of non-neurologic origin provoked no change in the serum aldolase level.

Acknowledgments: The authors acknowledge the cooperation of Dr. Abraham A. Rabiner, Dr. Abram Kanof and Dr. Nathan Epstein for their aid in diagnosis and selection of patients for this study, and Mr. Abraham Saifer for advice in biochemical determinations.

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Combined Staff Clinic

Current Views on Pathogenesis and Therapy of Rheumatic Fever

THESE are stenotyped reports of Combined Staff Clinics of the College of Physicians and Surgeons, Columbia University, and the Presbyterian Hospital, New York. The clinics, designed to integrate basic mechanisms of disease with problems of diagnosis and treatment, are conducted under the auspices of the Department of Medicine. The reports are edited by Dr. Richard J. Cross.

DR. DANIEL L. LARSON: Pioneer studies, notably those of Coburn, established that the overwhelming majority of attacks of acute rheumatic fever are preceded by a hemolytic streptococcal infection.[1] That there is a relationship between hemolytic streptococcus infection and acute rheumatic fever has since been demonstrated by data derived from a variety of epidemiologic, bacteriologic, immunologic and prophylactic studies. As this concept has now been generally accepted, it does not seem necessary to review the evidence for it in this Clinic.

We shall begin instead with a consideration of the pathogenesis of rheumatic fever. It would be nice, were it possible, to initiate such a discussion in orderly fashion by identifying the initial site of injury but unfortunately there is no definite information on this point. It is quite possible that the initial site of injury is remote from the tissues which, when involved, give symptoms of clinical significance. It may be that the primary lesion is located in or around the walls of small blood vessels. We must be content at the present time to rely upon evidence presented to us by pathologists about the site of *reaction* in rheumatic fever, even though we know little about the initial site of *injury*.

We shall therefore turn first to a discussion of the site of reaction, that is, the loose connective tissue. Loose connective tissue, as you know, occurs in many places in the body; it is found in the pericardium, the endocardium, the pleura and peritoneum; it surrounds blood vessels and nerves; and it forms the basement membrane of capillaries and of the glomerulus. It has been estimated that the total mass of this loose connective tissue in the body is approximately equal to that of the liver.

In the usual classification of loose connective tissue, it is divided into three components: fibrillar, cellular and the ground substances. Each of these will be discussed in a little more detail.[2]

The first of the fibrillar components we might discuss is collagen. (Table 1.) Collagen may be

TABLE 1
FIBRILLAR COMPONENTS

Collagen:
"Albuminoid" associated with carbohydrate
Polypeptide with 650 Å units
Source, fibroblast
Swells with acid, alkali, injury
Attacked at acid pH by pepsin
Vitamin C for repair and maintenance
Elastin:
"Albuminoid," refractile, elastic
Yellow, branches, anastomoses
Resists alkali, boiling
"Elastase" in crude trypsin
Reticulin:
Source not collagen fibrils; histochemically, refractivity and staining characteristics different

defined as a group of substances which, in the presence of acid, give rise to gelatin. They are associated with carbohydrate. Electron microscope studies indicate that the polypeptides constituting collagen have repeating units of 640 Ångstroms. The source of the collagen fibrils is, in all probability, the fibroblast. Characteristically, these fibrils swell in the presence of acid or alkali, or following injury. They are attacked by pepsin at an acid pH. Vitamin C apparently is necessary for their repair following injury and for their maintenance.

Elastin, the second fibrillar component (Table

1), is refractile and has a yellowish color. The fibrils characteristically branch and anastomose. In contrast to collagen, elastin resists alkali and boiling. Crude trypsin derived from hog sources contains an enzyme called "elastase" which shows activity against elastin.

TABLE II
GROUND SUBSTANCES

Hyaluronic acid:		
Source—in bacteria, only streptococcus groups A and C		
Composed of disaccharide		
N-acetyl glucosamine		
Glucuronic acid		
Testicular hyaluronidase		
Forms tetrasaccharide		
Pneumococcal and streptococcus hyaluronidase		
Forms unsaturated disaccharide		
Not antigenic		
Chondroitin sulphate A:		
Recovered from hyaline cartilage, bone, ligamentum nuchae		
Molecular weight 200,000		
Testicular hyaluronidase		
Forms tetrasaccharide		
Chondroitin sulphate:	B	C
Skin	+	0
Umbilical cord	0	+
Resistant to hyaluronidase	+	0
Both found in tendon, heart valve and aorta.		
Equimolar concentrations of:		
Galactosamine, uronic acid and sulphate.		

Reticulin was originally thought to be composed of collagen fibrils. It has been shown by means of histochemical technics, refractivity studies and differential staining that this is probably not the case.

The chemistry of the ground substance was almost unexplored until about twenty years ago. Since that time several groups of workers, particularly Dr. Karl Meyer and his associates, have gathered an impressive amount of information in this field.

Hyaluronic acid is one of the ground substances and is widely distributed in all animal tissues. (Table II.) In microorganisms it occurs, apparently, only in streptococcus groups A and C. Hyaluronic acid is composed of equimolar concentrations of N-acetyl glucosamine and glucuronic acid. It is split by hyaluronidase from bacterial sources to a tetrasaccharide, by testicular hyaluronidase to an unsaturated disaccharide. Hyaluronic acid is not antigenic in man or animal. This is in contrast to the hyaluronidase of bacterial origin, which is quite antigenic in man.

The second group of ground substances about which we have a good deal of information is the chondroitin sulfates. Three have been studied in some detail. In general, they can be differentiated on the basis of their reaction with hyaluronidase and by their distribution. Chondroitin sulfate A has been isolated from hyaline cartilage, has a molecular weight of 200,000, and, in the presence of testicular hyaluronidase, forms a tetrasaccharide. Chondroitin sulfate B and C can be differentiated on the basis of their tissue of origin, but both are found in tendon, heart valve and aorta. Analysis of these chondroitin sulfates indicates that they contain galactosamine, uronic acid and sulfate in equimolar concentrations.

Connective tissue reacts to injury in a limited number of ways. In general, there is an increase in metachromasia and some dispersion of the collagen fibrils. Quite frequently, one sees a deposit of substances called "fibrinoid" in the ground substance. The source of this fibrinoid is unknown. It was thought originally to be a specific reaction in diseases of the "rheumatic state," such as rheumatic fever and rheumatoid arthritis. It has since been shown rather convincingly that fibrinoid appears non-specifically following injury. Fibrinoid probably does not originate from collagen fibrils. It may appear in the placenta, for example, in areas where there are no collagen fibers. Hydroxyproline is one of the amino acids characteristic of collagen; however, fibrinoid from excised subcutaneous nodules does not contain hydroxyproline in amounts one would expect if it were derived from collagen fibrils.

Turning to the mechanisms by which the reaction may occur in the connective tissue, one is immediately faced with the fact that rheumatic fever, with the clinical course seen in man, has never been produced in an experimental animal. This immediately poses a good many problems in attempting to unravel the sequence of events which occurs in the pathogenesis of the disease.

For purposes of discussion one may divide the possible mechanisms of connective tissue injury into several categories, the direct effect of the living streptococcus being one, the toxic effect of streptococcal products another, and finally, as a third category, the various immunologic technics which have been used to

produce connective tissue damage. No attempt will be made to review the vast literature relating to the production of connective tissue injury. A few examples have been selected, however, to illustrate the type of information resulting from the use of several different investigative technics.

In considering the direct effect of streptococcal infection on the development of connective tissue injury, one must first recognize that the only known important natural reservoir for group A hemolytic streptococcus is man. Therefore, when you induce an infection with this organism in an animal you have created a highly artificial state of affairs. This must be remembered in interpreting data on streptococcal infections in animals.

Murphy and Swift[3] produced chronic streptococcal skin infections in rabbits and showed that approximately half of the infected animals had bacteremia, 20 per cent had acute rheumatic-like lesions and a smaller percentage showed scarring and rheumatic-type arteritis. This work was confirmed by Kirschner.[4] More recently, Glaser[5] produced Group A hemolytic streptococcic pharyngeal infections in rabbits. Seven of eight of the rabbits so infected showed dispersion of collagen fibrils and focal myocardial necrosis. Each of five animals sacrificed at the end of seven days showed the same changes in the myocardium.

Catanzaro et al.[6] studied a group of human subjects who had hemolytic streptococcal throat infections which were not treated until nine days after onset of the disease. Although there was no inhibition of early antibody response to the streptococcus these patients had a reduced attack rate of rheumatic fever as compared with the untreated controls.

These observations raise the question of the role of the living organisms as an essential mechanism in the development of acute rheumatic fever. They do not, however, provide satisfactory answers to certain questions: the severity of the streptococcal infection and the severity of the ensuing acute rheumatic fever do not parallel one another; one cannot explain the so-called "sterile exacerbations" seen frequently in recurrent rheumatic fever; one cannot explain the fact that approximately half of the adults with rheumatic heart disease have no history of acute rheumatic fever or of a streptococcal infection. Equally puzzling is the report of Stollerman[7] that in rheumatic children receiving penicillin prophylaxis and being kept free from streptococcal pharyngitis for periods as long as six months erythema marginatum or chorea may then develop.

In discussing some of the work that has been done on the direct toxic effect of streptococcal products, it is proper to point out that many of these experiments have been carried out with bacterial filtrates from streptococci grown *in vitro*. The conditions which obtain for streptococci grown *in vitro* do not necessarily apply when they have been grown in the human pharynx.

Of the two streptolysins produced by streptococci, streptolysin "O" is quite antigenic in man whereas streptolysin "S" presumably is non-antigenic. They can be further differentiated by certain growth requirements and reactions in the presence of oxygen. Bernheimer[8] was able to show that the isolated frog heart contracts violently after the direct administration of streptolysin O. In further investigations of the toxic actions of streptolysin, Thomas[9] produced a chronic streptococcal skin infection in rabbits that was capable of preparing these animals for what he designated a generalized Shwartzman reaction. Upon subsequent injection of a bacterial filtrate myocardial necrosis and severe renal damage developed in these rabbits.

Watson[10] produced streptococcal skin infections in rabbits, then excised the infected areas and isolated a soluble extract from the tissues. The extract was capable of sensitizing rabbits so that upon the subsequent injection of streptococcal filtrate containing streptolysin O the animals exhibited a generalized Shwartzman reaction. The conditions of this experiment fulfilled the requirements for production of this reaction, in the absence of any provocative agent but streptococci or streptococcal products.

Another interesting product of the streptococcus is proteinase. It shows activity against "M" protein, streptokinase and probably hyaluronidase. Kellner[11] injected crystalline proteinase into guinea pigs, rabbits and mice, and was able to demonstrate focal myocardial necrosis in a high percentage of the animals.

It is of interest that streptokinase is produced by relatively few organisms. Among them are hemolytic streptococci groups A and C, and possibly some strains of staphylococci and clostridia. This material may be responsible for the spreading phenomenon of streptococci

in vivo. Kellner has reported[12] that streptokinase injected into a group of mice induced widespread myocardial damage and skeletal muscle damage. However, similar results could be obtained using other proteolytic enzymes such as papain, trypsin and pepsin. Tillett[13] has shown that small amounts of streptokinase injected intravenously into human subjects causes hypotension, fever and some increase in fibrinolytic activity, but no evidence of other connective tissue damage was observed.

In general, experiments carried out in this fashion employ dosages of these toxins which are usually in excess of those one might expect to encounter in a natural infection. Furthermore, the distribution of lesions is somewhat different, and they are not progressive. Often the changes can be demonstrated within hours rather than the ten-to-fourteen-day interval seen clinically. If a direct toxic action is essential in the pathogenesis of the disease, one cannot explain the failure of about one-half of the patients with a previous episode of rheumatic fever to have an exacerbation following a fresh encounter with the organism. The delayed therapy studies of Catanzarro could be interpreted as indicating that the toxic effect of the organisms is not of much importance. These individuals were exposed to the toxins for as long as nine days without rheumatic fever developing at the expected rate.

Turning to the immunologic technics that have been used as tools for the production of connective tissue injury, one encounters a massive and somewhat bewildering accumulation of data in the literature. Perhaps it would help us in our thinking if we had a clear idea of the classification of the immunologic technics which are available to the investigator working on this problem. (Table III.)

One may divide antigen-antibody reactions into those with antigens of external origin and antigens of internal origin. Among the reactions associated with external sources of antigen, those requiring circulating antibodies include "serum sickness," hay fever, skin-sensitizing antibody and angioneurotic edema. The laboratory models used to try to reproduce this type of lesion are the Arthus reaction and local or generalized anaphylaxis. The Arthus reaction has been shown to be dependent upon precipitable circulating antibody, whereas anaphylaxis is apparently independent of macroscopically detectable circulating antibody.

There is another group of antibodies associated with antigens of external origin which have a high affinity for tissue. They are commonly referred to as "tissue-fixed antibody." These antibodies cannot be passively transferred with serum from a sensitized host. Contact dermatitis and some of the drug allergies are examples of this type of reaction. The laboratory model which may be used to produce a necrotizing progressive connective tissue lesion is the tuberculin type of reaction or "delayed" skin sensitivity.

Table III

EXTERNAL SOURCES OF ANTIGEN
Circulating:
Clinical
Serum sickness, hay fever, skin-sensitizing antibody, asthma, angio-edema
Laboratory model
Arthus reaction, anaphylaxis
"Tissue-fixed" antibody:
Clinical
Contact dermatitis, drug allergies
Laboratory model
Tuberculin-type or "delayed" skin sensitivity
INTERNAL SOURCES OF ANTIGEN
"Autoantibody":
Antigen residing in the host
Clinical
Donath-Landsteiner reaction
Some acquired hemolytic anemias
? Some thrombopenic purpuras
Laboratory model
Requires adjuvant, as in allergic encephalomyelitis
"Isoantibody":
Antigen in homologous species
Clinical
Erythroblastosis
Some blood transfusion reactions
Sloughing of homologous skin grafts
Laboratory model
Organ antibodies; adjuvants often required

Reactions involving antigens of internal origin are described as autoantibodies or autoimmune phenomena. Clinically, the Donath-Landsteiner reaction, some of the acquired hemolytic anemias, and perhaps some of the thrombopenic purpuras fall into this group. The experimental production of autoantibodies has not been very successful except with the use of adjuvants.

Isoantibody implies that the source of antigen resides within another host of the same species.

This type of reaction is more commonly encountered than autoimmune phenomena. Clinically, erythroblastosis, some blood transfusions and sloughing of homologous skin grafts may be used as examples of isoantibody reactions. In contrast to the autoantibody systems, adjuvants often are not needed. In the laboratory, both organs and extracts of organs from the homologous species have been used as antigens in isoantibody systems.

For about a generation, people have been interested in the notion that rheumatic fever may be an allergic disease. This idea took its origin from observations on the analogies between rheumatic fever and the events occurring in the course of serum sickness. As far back as 1915 Longcope[14] injected rabbits intravenously and intraperitoneally with horse and rabbit serum and noted chronic, progressive myocardial lesions. Since that time a large number of substances have been injected into animals in an attempt to produce connective tissue injury resembling that seen in rheumatic fever. The injury so produced depends upon the amount of material used, its chemical composition, its toxicity, route of administration, the species used, and, perhaps most of all, the willingness of the pathologist to call the changes "rheumatic-like."

The Arthus phenomenon was produced in joints of rabbits by Freidberger as long ago as 1929 and concomitantly with this reaction in joints he noted myocardial lesions. Since then the Arthus type of reaction has been produced in the pericardium, the brain, the kidney and other organs. The Arthus phenomenon, as we have pointed out, appears to be dependent upon the level of circulating antibody. Clinical studies on the amount of antibody formed in those who acquire acute rheumatic fever and those who escape the disease have suggested that the rheumatic patient's antibody response to streptolysin is greater than that of the normal. However, it is very difficult to control the dosage of antigen in a natural infection. Quantitative immunologic studies by Quinn[15] and his collaborators have indicated that rheumatic subjects respond perfectly normally to pneumococcus capsular polysaccharides.

Chase in 1946 was able to demonstrate the passive transfer of tuberculin sensitivity using guinea pig white blood cells from a sensitized donor.[16] This type of delayed sensitivity, as already pointed out, cannot be passively transferred to a new host with *serum* from a sensitized donor. More recently Lawrence[17] has been able to demonstrate the passive transfer of generalized skin sensitivity to tuberculin and to streptococcal "M" protein in man. This was done not only with intact leukocytes but with leukocytes that had been disrupted in several ways. Furthermore, the tuberculin type of reactivity could be passively transferred with disrupted leukocytes that had been treated with ribonuclease and desoxyribonuclease.

A number of investigators have reported that they have demonstrated autoantibody formation in animals. Usually work of this type has not been confirmed by individuals in other laboratories. More recently, Kabat[18] has been able to demonstrate, with the use of adjuvants, autoantibody formation in central nervous system tissue in monkeys. This represents an important advance in our understanding of possible mechanisms for the chronicity and exacerbations of a necrotizing lesion such as one encounters in rheumatic fever.

Some authors have attempted to produce antibodies to substances isolated from connective tissue, such as chondroitin sulfate, hyaluronic acid or collagen. In no case has antigenicity been demonstrated, either in the homologous or heterologous species. The few reports that have been published claiming the detection of antibody to ground substances are either unconfirmed as yet or workers in other laboratories have been unable to obtain similar results.

A vast amount of data on the antibodies to organs and organ extracts of heterologous species has been acquired. Among the people who have been working in this field are Masugi, Smadel, Seegal and Pressman. They have uncovered an important body of information on the conditions necessary to produce connective tissue damage, particularly with respect to the kidney. They have also demonstrated the chemical similarity of certain groupings in antigens derived from heterologous species. At the present time it would seem that similar studies on the production of autoantibodies will yield additional valuable information.

In summary, a hemolytic streptococcus infection is, without doubt, a necessary antecedent to the onset of acute rheumatic fever. We have very little information on the initial site of injury but we do have some information on the sites of reaction in connective tissue. A great

deal has been learned about the constituents of ground substance but there almost certainly are materials present which have not yet been isolated or characterized. We have even less information on the complex reaction between the hemolytic streptococcus and the host's connective tissues. We can be hopeful that more knowledge will soon be made available on this problem as a result of work on the role of the living streptococcus, the role of streptococcal products, and the role of immunologic reactions.

The clinician is frequently faced with the problem of deciding whether a patient has rheumatic activity or not. Dr. Fischel, who is Medical Director of The Bronx Hospital, will now discuss some of the considerations in the diagnosis of rheumatic fever in the absence of the usual parameters of the disease.

DR. EDWARD E. FISCHEL: The textbook description of the manifestations of rheumatic fever has not undergone any important revision since the early descriptions of Bouillaud and Cheadle. In 1835 Bouillaud emphasized the association of cardiac disease with childhood rheumatism, and in France today the disease still bears his name. The most eloquent description of the disease was by Cheadle in 1889. His small monograph attached importance to the association of an upper respiratory tract infection with manifestations of fever, polyarthritis, cardiac involvement, rash, nodules and other signs of the disease.

It is rather discouraging to realize that knowledge of the disease has not advanced sufficiently in the last sixty-odd years to permit a more physiologic basis for diagnosis than the critical accounting of the various manifestations of the disease. Many of the manifestations are not pathognomonic, and all are difficult to measure with any degree of precision.

Definitive standards, generally acceptable, are desirable despite the availability of rather arbitrary criteria set up by individual physicians pursuing isolated projects. Perhaps the most widely accepted criteria are those formulated into major and minor manifestations by the late Duckett Jones. As modified by a committee of the American Heart Association, the major diagnostic criteria include carditis, polyarthritis, chorea, subcutaneous nodules and erythema marginatum. Minor criteria include fever, arthralgia, prolonged P-R interval in the electrocardiogram, increased erythrocyte sedimentation rate, elevated white blood count, presence of C-reactive protein, evidence of a preceding beta hemolytic streptococcal infection and evidence of previous rheumatic fever or rheumatic heart disease.

These criteria have been discussed at length by various authors, and I would refer you to your textbooks for further elaboration of the various individual manifestations, with two exceptions. It is readily apparent that carditis, perhaps the most important of these manifestations, is the one that lends itself least to detection by objective or quantitative means. It is also apparent that "evidence of preceding streptococcal infection," while considered a minor manifestation from the point of view of specificity for the diagnosis of rheumatic fever, is nevertheless a major factor in the development of the disease. It is the recognition of this relationship that constitutes the major advance since Cheadle's time in our understanding of the disease and permits us to broaden our horizon in a consideration of it.

When a disease is first recognized as a clinical entity, emphasis is placed on its more dramatic and more severe manifestations. It is well known that rheumatic fever may occur without fever and without rheumatics. By restricting ourselves to the more obvious manifestations we may exclude many mild as well as severe forms of the disease. Patients with very mild rheumatic fever may not be conscious of any discomfort and may not seek the help of a physician.

The occurrence of such subclinical attacks may be inferred from three chief lines of evidence. The first deals with the sequelae of streptococcal sore throat, which may frequently approximate the picture of rheumatic fever although, clinically, we may not wish to define these sequelae as rheumatic fever. The second is the frequency with which rheumatic heart disease is found in adults who give no history of an acute illness suggesting an acute rheumatic attack. The third line of evidence is in the many autopsy surveys which indicate a high frequency of rheumatic heart lesions in serial autopsies.

The first of these, the occurrence of rheumatic-like sequelae of streptococcal infections, was defined by at least two studies during the last war. In Navy personnel, Watson, Rothbard and Swift[19] studied 110 patients with scarlet fever and followed them closely after they recovered from that disease. Sixty-three patients had no sequelae, twenty-nine had purulent

complications. If we discount those with purulent complications alone, twenty-two patients were found to have some electrocardiographic abnormality. Four patients had both purulent complications and electrocardiographic abnormalities. Eight of the twenty-two patients had classic rheumatic fever, another eleven had signs and symptoms which were "qualitatively but not quantitatively similar to rheumatic fever," to cite the well-chosen words of the authors.

The Army made a similar study of 183 patients with streptococcal pharyngitis. Rantz and his coworkers[20] found that 27 per cent of the 183 patients had some manifestations of what they termed "continuing disease"; sixteen patients, or 9 per cent, had clinically overt rheumatic fever, while 18 per cent had similar manifestations of a less striking nature, including arthralgias, fever, elevated erythrocyte sedimentation rate for an unusual length of time and other vague phenomena. Electrocardiographic abnormalities occurred in thirty-one patients, only nine of whom had typical rheumatic activity.

Such minor manifestations may not warrant the label of rheumatic fever, with its attendant concern and complex management and prophylaxis. But neither should such abnormalities be discarded casually as non-rheumatic. A judicial period of re-evaluation may be more satisfactory than taking an immediate position on either side of the fence.

In a provocative report, Weinstein[21] studied 167 patients with scarlet fever who had been treated with penicillin. The details of selection, timing, dosage, diagnosis and follow-up must be omitted here for the sake of brevity. Suffice it to note, ten patients had prolonged conduction time by electrocardiograph, while only two had clinically overt rheumatic fever. Seven years later, 110 of the original group were reassembled and reviewed. A hundred patients who had had no previous electrocardiographic abnormality had no evidence of heart disease; eight of the ten patients who were followed and had had previous electrocardiographic abnormalities now had stigmata of rheumatic heart disease. Under the conditions of this study, repeated attacks of rheumatic fever may have occurred and there may have been repeated streptococcal infections but rheumatic heart disease may well have developed after only minor manifestations during one attack in some of these patients.

Inadequate detection of the disease is apparent also from studies of late heart disease. There is a substantial incidence of rheumatic heart disease in adults who have had no history of previous rheumatic fever. This has been well documented in patients of both sexes undergoing mitral commissurotomy. In women, a study at the Boston Lying-in Hospital showed that fully one-third of the patients did not give a history of rheumatic fever.[22] Relevant data in young men were accumulated during World War II. Re-examination[23] in four cities of 2,205 rejectees rejected from military service because of rheumatic heart disease showed that only 15 to 50 per cent gave a history of rheumatic fever. Inadequacy of histories may explain some of these figures but the general trend is obvious.

Finally, inadequate clinical detection of rheumatic fever is apparent in an appraisal of autopsy surveys. The reported incidence of rheumatic heart lesions in several series varies widely, from 11 to as much as 90 per cent, depending in great part on the morphologic criteria employed. It is readily apparent, no matter what the figure is, that frank rheumatic heart disease, and less classic rheumatic-like lesions, occur more frequently than we suspect clinically. All these data should serve to make us more humble in estimating our ability to detect the disease.

Several laboratory tests may be of aid in the recognition of rheumatic fever, although none are specific for the disease. Broadly stated, from the pathogenetic point of view rheumatic fever is a sterile, inflammatory process which follows a streptococcal infection. It is not the only such process, since acute glomerular nephritis and perhaps less well-defined entities also share in this characterization. The laboratory may be useful in two general respects. First, to help establish the occurrence of a previous streptococcal infection; and, secondly, to aid in determining the presence of an inflammatory process.

Of the specific streptococcal antibodies, one of the most commonly determined is the antistreptolysin titer. In about 80 per cent of the patients with streptococcal infection a rise in titer will occur irrespective of whether or not rheumatic fever develops. The antistreptolysin titer may be higher in rheumatic patients than in non-rheumatics when large numbers of patients are studied and purulent complications are minimal. However, in individual patients

the titer can be used only to establish the occurrence of a previous streptococcal infection. The same may be said of other antibodies to streptococcal products which have been studied, such as antistreptokinase, antistreptococcal hyaluronidase, the C-carbohydrate antibody and other such fractions.

TABLE IV
SOME CHANGES IN THE SERUM ASSOCIATED WITH INFLAMMATION

Fibrinogen	Zinc turbidity
Alpha globulin	Formol gel
Gamma globulin	Serum copper
Complement	Takata-Ara
C-reactive protein	False positive Wassermann
Trypsin inhibitor	Methylene blue reduction
Plasmin	Cryoglobulins
Hyaluronidase inhibitor	Weltmann coagulation band
Bactericidal substances	Iodoacetic acid index
Ceruloplasmin	Lipids, cholesterol
Erythrocyte sedimentation rate	Vitamins A, C
Hexosamine	Transferritin
Mucoprotein	Serum iron
Quaternary ammonium salt reactant	Transaminase
	Diphenylamine reaction

A second group of laboratory aids is commonly spoken of as "non-specific." The group is specific for any inflammatory reaction, whether or not it is rheumatic.

A large number of changes occurs in the serum during inflammation; many of these are listed in Table IV. Only a few have achieved any widespread popularity as a measure of inflammatory reaction. At various times one or another, such as the Weltmann coagulation band and, currently, the C-reactive protein test, have achieved some degree of popularity. The peculiar activity of the C-reactive protein, of serum complement, transferritin and other substances is of considerable theoretic interest in a study of inflammation.

Perhaps the simplest and most generally reliable test to appraise inflammation clinically is the erythrocyte sedimentation rate. Although it has been stated that the rough quantitative measure it gives is less desirable than a simple positive or negative result, this would be possible only with loss of sensitivity of the test. It is, of course, wholly illogical to use any of these tests to attempt to differentiate the inflammation of rheumatic fever from that of rheumatoid arthritis, subacute bacterial endocarditis, penicillin sensitivity, purulent sinusitis or a variety of other inflammatory disorders. Although relatively specific for inflammation, these tests have no respect for the etiology of such inflammation.

There is, of course, reluctance among some physicians to stigmatize a child with the label "rheumatic fever." To avoid this such terms as "toxic arthritis following scarlet fever" have been employed and the patient is not protected from subsequent attacks by prophylactic measures. On the other hand, transient fever in a child with a soft systolic murmur ought not be considered rheumatic until considerable confirmatory data are available, in the history, in the remainder of the physical examination, in the laboratory data, and in the follow-up.

Advances in the study of rheumatic fever may result in a broader concept of the disease so that many of its milder characteristics may be included. In that event the physician will have the responsibility of educating patients and their families to the fact that mild attacks do occur, and that prolonged bed rest and indiscriminate restriction of physical activities are not invariably necessary once the term "rheumatic fever" is used.

Management of the patient with subclinical or possible rheumatic fever poses many questions, but few are insurmountable if individual circumstances are weighed. In most obscure situations, the problems usually are not so urgent as to require immediate solution without some degree of follow-up and judicious reappraisal.

DR. LARSON: Thank you, Dr. Fischel. The point that Dr. Fischel made, of using a little common sense in the management of the patient who may have rheumatic fever, becomes considerably more important in view of the recent publication of the New York Heart Association recommending lifetime prophylactic therapy for those who have rheumatic fever. Good judgment is necessary in this situation.

Many studies have been published on the management of patients with rheumatic fever. Unfortunately, the criteria employed in selection of cases are not always sufficient to reduce the likelihood of bias in the testing of a therapeutic regimen. Dr. Frank, who is Assistant Professor of Medicine at the Albert Einstein Medical School, will now tell us something of the results obtained in a carefully worked out study comparing three different therapeutic agents in the management of rheumatic fever.

DR. CHARLES W. FRANK: The relative value of salicylates and the adrenal hormones in the

management of rheumatic fever has been debated for these past several years, much as the use of salicylates *per se* had been argued for decades before.

It is disappointing to reflect how much of the work which has gone into solving this problem has apparently been diverted into heat energy rather than light. Clinical experience has indicated that each of these agents certainly is of use in the majority of patients with rheumatic fever, and satisfactory or even dramatic results have been obtained by all investigators with each of these agents. But failure to achieve uniform success, especially in the more critically ill child, and failure to prevent the development and progression of chronic rheumatic heart disease once established, points up the inadequacy of all therapies so far tested.

To assess the relative merits of one agent over another in any dose plan poses a problem in quantitative analysis which cannot be easily solved. Too often, clinical studies have been ill-conceived efforts resulting in data which cannot be logically interpreted. Although the necessity for a control group is often accepted, it is commonly assumed that the inclusion of any large number of untreated patients automatically provides an adequate control. Of course, this is absurd. The requisites for a clinical trial have not been sufficiently emphasized.

To determine the clinical effectiveness of any therapeutic program requires, first, a patient-sample representative of the disease to be studied. Thus strict diagnostic criteria must be selected and established to ensure that the observed results are pertinent to the disease being treated. The sample of patients, naturally, must be large enough to permit division into control and treatment groups, and each group should be large enough to minimize the importance of physiologic as well as chance variations.

Of utmost importance, the two groups—treated and control—must be comparable with respect to all factors known or thought to be of importance in the outcome of an individual attack. Thus, with reference specifically to rheumatic fever, the duration of illness prior to the onset of therapy, the type and severity of the presenting signs and symptoms, the history of prior rheumatic fever and prior heart disease, and the age of the patient have all been thought, and can now be shown, to be important factors influencing the outcome of the individual attack. If the two groups are not equally represented by patients of similar type, one cannot expect the outcome to reflect only the difference in therapeutic agents. Failure to achieve such comparability of the treated and control groups is probably the most common serious error of methodology in published clinical reports of so-called controlled studies, and is very likely responsible in large part for the apparently divergent results in the literature.

Aware of these problems in clinical studies, and appreciative of the fact that an adequate number of patients for a clinical trial of ACTH, cortisone and salicylate in the treatment of acute rheumatic fever would require pooling of the patient populations of many hospitals, a group of investigators joined together in 1950 in a Cooperative Study established in such a way as to satisfy these criteria. The response of 497 children to a specified six-week course of ACTH, cortisone or salicylate, and the status of these patients one year later has been reported.[24] Some of the results of that study should be emphasized.

Fever, arthritis and tachycardia subsided promptly in response to all three agents. This result is so regularly observed that one should suspect another disease or inadequate dosage if these manifestations persist. Recurrence commonly followed the cessation of therapy after six weeks—the "rebound." The erythrocyte sedimentation rate fell more rapidly in the two hormone-treated groups than in the salicylate-treated patients. However, by the end of six weeks of therapy all three groups were similar with respect to this test. The rebound in sedimentation rate was more striking in the hormone groups but one month later all groups were again alike in this respect.

Nodules have attracted the attention of many investigators in rheumatic fever, not because they are common, for they are rather uncommon manifestations, but because they have been looked upon as the subcutaneous replica of the lesion which exists in the heart. The hope was that the disappearance of nodules under the skin would be accompanied by the disappearance of nodules in the heart. There is a tendency for more rapid disappearance of subcutaneous nodules in those patients treated with the hormones than in those patients treated with aspirin but this is not striking. Nodules persisted in all groups, indeed new nodules appeared even under the influence of full therapeutic doses of all three agents.

When one comes to appraise the effects of

these drugs on the heart, major difficulties arise. How can one tell when carditis is responding? Investigators in different reports have relied on varying criteria. Some may be impressed by a variable heart rate, by the character of the heart sounds, by the presence of a gallop rhythm, by the changing quality of murmurs, by minor changes in heart size or alterations of the electrocardiogram. Unfortunately, however, many of these indices are so subtle and so subjective that they are not susceptible to quantitative study. Certain cardiac manifestations can be and were analyzed in the Cooperative Study.

The patients who received ACTH and cortisone exhibited a more rapid shortening of the P-R interval than did those who were given salicylate. Indeed, the P-R interval was shorter in the hormone-treated patients during the second week of therapy than it was in these same patients one year later when rheumatic fever was no longer active by clinical criteria. This has suggested the possibility that the hormones have some specific effect on conduction through the AV node. This is still an open question.

The response of the patients with the more severe attacks of rheumatic carditis was examined with special interest. Would acute pericarditis subside more promptly under the influence of the hormones? After the second week of therapy most of the patients who had pericarditis initially were improved in all three treatment groups. There was no striking difference in the rate at which this improvement occurred and there were some failures in all. Pericarditis appeared for the first time in certain patients under all forms of therapy. Similarly, congestive failure was usually relieved after three weeks in all groups and there was no difference noted in the rate at which this was achieved. Some failures occurred in all groups. Six of the 497 children succumbed to the attack. Three were treated with aspirin and three with hormones.

Finally, the response of cardiac murmurs was carefully analyzed in many ways. The softer apical systolic murmurs disappeared more promptly in the hormone-treated patients. However, this was but a temporary advantage. More interest rests in the status of the patients one year after completion of treatment. Irrespective of the therapy employed, the best follow-up results were observed in those children treated early in their first attack of rheumatic fever, especially when clinical signs of cardiac involvement were minimal or absent at the time therapy was begun. Delay of treatment, the presence of certain specified signs of carditis or the history of prior rheumatic involvement each appeared to result in a much higher incidence of cardiac murmurs in the follow-up period. The design of the Cooperative Study resulted in an even distribution of these three important factors among the treatment groups, thus cancelling their influence on the outcome of therapy. In this study sample, approximately half of the children were free of significant murmurs one year after treatment, whether the agent employed was ACTH, cortisone or salicylate. Thus no long-term benefit appeared to result from the use of hormonal therapy.

It should be emphasized that these results apply to the treatment plan used in the study. For the moment, then, let us look at the dosage of hormones. ACTH administration was begun at 120 units per day and was decreased stepwise over a six-week period, for a total of 2,460 units. Cortisone therapy was begun at 300 mg. for the first day, 200 mg. the next four days and decreased for a total of 4.1 gm. given over a six-week period. This dosage was selected in 1950 at a round-table discussion among investigators, with the best information then available. Although it has been implied by some that this is an inadequate dosage, ninety per cent of the children so treated showed clinical signs of the hyperadrenal syndrome. Investigators who have claimed more beneficial results with the hormones have often used considerably less hormone than this.

The question might be asked, however, what would the results have been if more hormone had been given? Naturally, this study cannot answer that. Two recent reports of the use of considerably larger amounts of cortisone in first attacks of acute carditis are of interest. Greenman et al.[25] reported on fifty-five children given 300 mg. of cortisone daily for six weeks. There were two deaths and about half had normal hearts at three months to three years. Markowitz and Kutner[26] varied their dosage somewhat, averaging 200 to 300 mg. per day for six weeks, tapering for three weeks more, and in some patients continuing with 50 mg. per day for two to ten months. Of forty patients so treated, sixty-five per cent were free of apparent heart disease at follow-up. Neither of these two studies was controlled. It has not been demon-

strated that these results are any better than one might have expected with the dosage of cortisone or, indeed, even the dosage of salicylate used in the Cooperative Study.

It is only fair to point out that, as the dosage and duration of cortisone are increased, one will encounter degrees of hyperadrenalism which the rheumatic child will not tolerate. The toxic effects reported in the two papers of Greenman and Markowitz are impressive. Hypertension appeared in a considerable number; in one child seizures developed. Infections, in the form of cellulitis, stomatitis and pneumonia, were common. Psychiatric disturbances were troublesome. Depression was common and one of Greenman's patients attempted suicide. In one of Markowitz's patients catatonia occurred. Evidently there are substantial difficulties in such heavy dose hormonal therapy in the treatment of rheumatic fever in children.

What clues can we gain from these and other studies, then, to guide us in our choice of a therapeutic agent for a given patient with rheumatic fever? I believe that the Cooperative Study data emphasize the importance of early diagnosis and therapy. If a patient happens to be seen early in the course of the disease, before a significant cardiac murmur is present, the outcome with salicylate alone is so uniformly good that this is probably the therapy of choice.

However, when acute carditis is present it would seem reasonable to add the adrenal steroids. Although no obvious benefit could be demonstrated in the Cooperative Study, our tools for measurement are gross, and it may be that addition of the steroids in individual patients will be of some benefit; at least, the physician can hope so. The surprising safety of short courses of the adrenal steroids helps to justify this viewpoint.

Although therapy of the acute attack leaves much to be desired, it may have an important effect on the future course of the disease. As you all well know, rheumatic fever is a recurring illness and three of four children who survive the initial attack can be expected to have a recurrent attack. The recurrence rate in some series has been found as high as 15 per cent per year for at least the first few years following the initial attack.[27]

It has been shown abundantly that at least 90 per cent of these recurrent attacks can be prevented by continued prophylaxis against streptococcal infection. It is reasonable to expect that prevention of these recurrences will minimize the degree of ultimate cardiac damage.

DR. LARSON: There are several points which have not been touched upon, because of the scope of this subject, and I wonder if there are any comments or questions from the audience.

DR. HENRY ARANOW: I should like to ask about the epidemiology of inapparent rheumatic infection which is diagnosed only by the appearance of a cardiac lesion later in life. Does the incidence of this occult form of the disease have the same relationship to climate and other factors as does the occurrence of obvious, easily recognized, rheumatic fever?

DR. FISCHEL: That is a subject which has been studied in many respects. It is known that symptomatic rheumatic fever occurs less frequently in warm climates, at least is less frequently recognized. But the incidence of late rheumatic heart disease is apparently the same as in the rest of the country. This held true not only of the United States but also Panama, North Africa and various other tropical and subtropical areas of the world.

DR. ARANOW: Is there any reason why?

DR. FISCHEL: I know of no reason why. Dr. Beatrice Seegal did one of the classic studies in this respect years ago.[28] She might be able to tell us why rheumatic fever, or scarlet fever for that matter, is less common in some climates, even though the streptococcus is there.

DR. BEATRICE SEEGAL: I think you are optimistic, Dr. Fischel.

DR. FISCHEL: The interesting thing is that in warmer climates neither polyarthritis nor the erythematous rash seems to develop.

DR. FRANKLIN M. HANGER: May I ask a question about the antistreptolysin titer? Isn't it generally held that the rheumatic person maintains an elevated antistreptolysin titer longer than the average person following streptococcus infection?

DR. LARSON: In the delayed therapy studies of Rammelkamp, the antistreptolysin titers were comparable in those who received treatment at the end of nine days and in those who did not. But you are correct in stating that the antistreptolysin titer may fall more rapidly in those who have received therapy than in those who have not received therapy. The interpretation, however, is another thing. It is quite possible that the immunologist is measuring the wrong thing, that is, he is not dealing with

the antigen-antibody system operating in the pathogenesis of the disease.

DR. CHARLES RAGAN: Do you think that the L form of streptococcus has any place in this pathogenesis?

DR. LARSON: I do not think there is enough information available at this time to answer that question.

DR. PUTNAM LLOYD: Would you comment on the prolonged use of antibiotics in prophylaxis? Is it now agreed generally, for example, that that is the proper management?

DR. FRANK: What is the factual basis that we have to go on? We know the recurrence rate of rheumatic fever is high for four or five years following the initial attack. Before the days of prophylaxis, annual recurrence rates were as high as 15 per cent for the first two years after an attack. They then start to fall off. The attack rate of clinical rheumatic fever, after a group A streptococcus infection, in the general population is, roughly, 3 per cent. The attack rate following recovery from acute rheumatic fever is, roughly, 50 per cent. Now, the unanswered question is, does it stay 50 per cent in these patients for the rest of their lives, or does it gradually come back down to 3 per cent? If it does, then it would be reasonable to discontinue prophylaxis when it approaches that in the rest of the population. If it stays up, then it should be kept up for life.

We don't have the facts on which to base the answer. My personal prejudice would be guided by such factors as the severity of the heart lesion in the child involved and what I thought of the possibility of his exposures to streptococci. If you see a young child, living in overcrowded housing, who is going to be plagued with "strep" for the rest of his life, who has had a bad attack of rheumatic fever, with a cardiac lesion, I think it is fair to consider that this child must or should be kept on prophylaxis for the rest of his life. But if an adult has a minor attack, has no cardiac involvement, and is not going to live in an endemic area then I think there is considerable question as to the necessity for continued prophylaxis.

STUDENT: What is the recommended method of prophylaxis?

DR. FRANK: There are, in general, three methods that have been shown to be effective. One-half to one gram a day of sulfadiazine throughout the year is effective and remarkably well tolerated. Penicillin has certain theoretic advantages over sulfadiazine, one of them being that there are no group A streptococci which are resistant to penicillin. Occasional strains of streptococci are resistant to sulfadiazine.

Penicillin may be given either orally, a dose of 250,000 units a day, or as parenteral repository (N,N′-dibenzylethylene diamine dipenicillin G) in a dose of 1.2 million units intramuscularly at monthly intervals. Probably the major gap in oral prophylaxis is the failure of the patient to take the pill.

DR. ALFRED FISHMAN: Dr. Frank, in the Cooperative Study, therapy was carried out according to plan for a period of six weeks. At the end of that time therapy with either salicylates or hormones was terminated. A certain number of rebound phenomena were observed in both categories, if I am not mistaken, but I think this raises the question which always comes up in our minds: namely, how long should a child or an adult who is believed to have acute rheumatic fever remain under treatment?

DR. FRANK: There is no agreement on this point. Six weeks, we can say, is too short because we get a rebound when we stop. Why do we have the rebound? To many of us, the "rebound" means that the patient is still sick. Others interpret a rebound differently. There is no good reason to know which interpretation is correct. Some people, as you know, treat rheumatic fever for one week and ignore the rebound. Others maintain the treatment for six months or longer. How does one tell which is right? I don't know.

DR. RAGAN: What have you got to lose by continued salicylates?

DR. FISCHEL: That is part of the answer, I guess, Dr. Ragan. In reviewing the traditional approaches to therapy, before the hormones were introduced, we found that 85 per cent of those patients who were observed for sufficient periods of time following cessation of salicylate had some minor manifestations of a recurrence. In the therapy of the disease it seems axiomatic to suppress rheumatic inflammation as early as possible. If we extend this concept we would continue to prevent inflammatory reaction even late in the disease. In order to do that we like to continue salicylate medication with the understanding that the patient is not completely well. Salicylates are continued until the host can obliterate the disease. Perhaps the prolonged use of salicylate permits gradual defense mechanisms to build up. At any rate the re-

bound is less dramatic or more frequently absent after prolonged therapy. I do want to emphasize that the rebound period is not totally innocuous, although in most patients it seems to be. During the Cooperative Study one of the deaths occurred at the time cortisone was stopped. A full exacerbation, with failure, pulmonary edema and death occurred. Other patients had a recurrence of pericarditis when aspirin or cortisone was stopped. That is something which is rarely seen; in fact, we have been looking for it, to try to substantiate some therapeutic effect of salicylate in an area other than the joints. We have observed several instances of suppression of rheumatic pleuritis and peritonitis on successive reinstitution and withdrawal of salicylates.[29]

Again, perhaps as a personal prejudice, we like to continue the drug for at least a month or two after all signs have returned to normal; in the severe case at least two or three months may be better, and there appears to be no harm in doing that. Ambulation may be initiated with little risk of increased cardiac damage.

DR. FISHMAN: I wonder if you would amplify the evidence for a direct effect of salicylates on the inflammatory process?

DR. FISCHEL: The evidence for suppression of the inflammatory reaction early in the course of the disease never impressed anybody before cortisone was introduced because it was said, "Well, if you had put that rheumatic patient to bed, he would have gotten better anyhow." Acute manifestations, whether arthritis, fever, pleuritis or whatever, respond so well to aspirin that it seems illogical to use the term "masking." The pathogenesis of the disease is pretty much the same, whether it is in the synovia or in the heart valve, although it does not lead to scarring in the synovia. A peculiar concept of the disease has evolved, namely, that a drug will affect inflammation in one area and not in another. It is as though with a more specific disease and drug it were maintained that streptomycin affects tuberculosis of the lung but not of the joints.

Now, if the subsidence of inflamma n in association with drug therapy is not impr ve, consider the reverse situation. Discontin of the drug results in a flare-up of inflamma Then there is no question that the previou administered drug was suppressing tachycardia, if that recurs, or pericarditis, peritonitis, pleurisy, polyarthritis, fever, or the like.

Some patients do not have any arthritis, and when the rebound includes a recurrence of fever and elevated sedimentation rate we believe it reflects inflammation in some other area; the statistical chances are that there is inflammation in the heart.

DR. ROBERT F. LOEB: I must confess I am one of those sentimentalists who agree with Drs. Frank and Fischel that there is evidence of subsidence of the inflammatory process with the use of salicylates. If you include the change in conduction time in the heart, perhaps this also is evidence of reduction of edema, or something of that kind, in this area.

Dr. Kenneth Turner and Dr. Robert Levy, a good many years ago, studied the effects of salicylates on the P-R interval. It may not have been a properly controlled study but there appeared to be evidence that the P-R interval tended to be reduced under the influence of salicylate therapy; that this effect was not invariable, however, was borne out by a patient who was receiving 10 gm. of salicylate a day, with a significant depression of serum bicarbonate and development of the hyperventilation syndrome. Nevertheless acute pericarditis developed and a P-R interval which rose to about 0.28 seconds. In most cases, however, there is reason to believe that inflammation is suppressed. Is this all wrong, Dr. Ragan?

DR. RAGAN: I think it has been shown in some experimental models that, in the myocardium at least, salicylate is an anti-inflammatory agent. If you take arthritis induced by silver nitrate as a model, salicylate is much less potent, insofar as tolerance goes, than the steroids, but it is an anti-inflammatory agent. I think that is pretty well accepted.

SUMMARY

DR. RICHARD J. CROSS: It has long been known that rheumatic fever occurs as a result of an infection by the hemolytic streptococcus. The precise pathogenesis is far from clear but recent studies are beginning to shed some light on the relative importance of the living organisms, of their toxic products, and of the host's immune reaction to the infection. The chief site of reaction appears to be the loose connective tissue, and our understanding of the nature of rheumatic fever has been gravely handicapped by the inadequacy of our knowledge about this important tissue. Recent advances in our under-

standing of the biochemistry of connective tissue are now providing us with a clearer insight into the changes which occur in rheumatic fever and allied diseases.

The clinical picture of full-blown rheumatic fever is well known and easily recognized. It seems clear that the disease can also occur in a mild, subclinical form which is nonetheless quite capable of leading to disabling cardiac involvement. The availability of medical measures which will reduce the likelihood of such involvement makes urgent the recognition of these mild cases. In this task the physician may be aided by certain laboratory tests indicating a recent streptococcal infection or by other tests indicating the presence of an inflammatory reaction. But the most important factors in arriving at a correct conclusion are a careful appraisal of the entire clinical picture and the use of common sense, based on a familiarity with recent significant studies in this area.

The proper management of rheumatic fever has long been a controversial topic, largely because of failure to appreciate the great variability of the disease and because of neglect of control of the various factors which affect the prognosis. The recent, carefully controlled Cooperative Study comparing the effects of ACTH, cortisone and salicylates in rheumatic fever has shed considerable light on questions which previously generated chiefly heat. Regardless of which agent is employed, early diagnosis and treatment are apparently of prime importance. Rebound phenomena, often observed when a brief course of any of these agents is abruptly ended, can be largely avoided by long-continued salicylates, and there seems to be little disadvantage in doing this. The prolonged use of antibiotics to prevent recurrences is of great value in many instances, although one may question the wisdom of routine, lifetime prophylaxis for all rheumatics.

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Reviews

Fifteen Years' Experience with Staphylococcus Septicemia in a Large City Hospital*

Analysis of Fifty-five Cases in the Cincinnati General Hospital 1940 to 1954

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WHILE most bacterial infections in man are yielding increasingly to the pressure of an ever-growing legion of powerful chemotherapeutic agents, Staphylococcus aureus infections are waging stubborn rear-guard resistance. Numerous recent studies attest to this and emphasize the difficulty of successfully treating deep-seated staphylococcus infections [*1–9*].

Since the report of Hamburger and Ruegsegger [*10*] in 1941, fifty-five cases of established staphylococcus bloodstream infection have been seen at the Cincinnati General Hospital. In each instance either two or more positive blood cultures were obtained or established staphylococcus infection was confirmed by autopsy.

It is the purpose of this report to analyze the results of treatment in this group of patients and to discuss several clinical aspects of the disease.

INCIDENCE AND RESULTS OF TREATMENT

Table 1 presents the yearly incidence of cases between 1940 and 1954, with the number of patients with bacterial endocarditis and the number of deaths. Except for the two-year period 1945 and 1946 in which only one case was recorded, the annual incidence of this serious affliction has remained rather constant. Similarly, the proportion of patients with endocarditis is unchanging.

The mortality rate in the entire series was 71 per cent. From 1940 to 1947, when sulfonamides, penicillin and streptomycin were the only chemotherapeutic drugs available, 83 per cent of the patients died. Since 1948, when chlortetracycline and other agents became available, 62 per cent died. This disappointingly small decline in the mortality rate is similar to the experience of others [7]. The mortality rate

TABLE 1
INCIDENCE, INCIDENCE OF ENDOCARDITIS AND MORTALITY RATE OF STAPHYLOCOCCAL SEPTICEMIA AT THE CINCINNATI GENERAL HOSPITAL, 1940–1954

Year	Cases	Cases of Endocarditis	Deaths
1940*	2	1	2
1941	3	1	2
1942	5	4	5
1943	3	3	3
1944	7	4	4
1945	0	..	..
1946	1	0	1
1947	2	2	2
1948	3	1	1
1949	4	2	2
1950	6	4	4
1951	8	6	7
1952	3	1	2
1953	5	5	2
1954	3	1	2
Totals	55	35 (64%)	39 (71%)

* Incomplete year

* From the Infectious Disease Laboratory of the Department of Medicine, University of Cincinnati College of Medicine and the Cincinnati General Hospital and the Medical Service, Cincinnati Veterans Administration Hospital. This investigation was supported in part by grants from the National Heart Institute, National Institutes of Health, U. S. Public Health Service, Department of Health, Education and Welfare, the Holmes Research Fund and the Lederle Laboratories Division, American Cyanamid Company.

TABLE II

STAPHYLOCOCCAL SEPTICEMIA

RELATIONSHIP OF MISCELLANEOUS FACTORS TO SURVIVAL OR DEATH

	Patients Who Survived–16 Cases (median age: 30.5 yr.)		Patients Who Died–39 Cases (median age: 55.0 yr.)		Total–55 Cases (median age, 46.0 yr.)	
	No.	Per cent	No.	Per cent	No.	Per cent
On Admission:						
Fever >102°(F.)	12	75	25	64	37	67
Shock (BP <100 mm. Hg)*	1	7	4	11	5	10
Heart failure	0	.....	4	10	4	7
Hemiplegia	0	.....	4	10	4	7
Azotemia (BUN >60 mg. %)†	0	.....	2	6	2	5
Classification on admission‡						
Condition 2	8	50	9	23	17	31
Condition 3	6	50	20	77	26	69
Condition 4	2		10		12	
Endocarditis	10	62	25	64	35	64
Meningitis or Cerebritis	4	25	17	44	21	38
Other Serious Disease:	10	62	36‖	92	46‖	84
Chronic rheumatic heart disease	5	31	16	41	21	38
Other major heart disease	2	12	11	28	13	24
Diabetes mellitus	1	6	5	13	6	11
Cirrhosis of liver	1	6	4	10	5	9
Obstructive uropathy with infection	0	.....	5	13	5	9
Miscellaneous conditions§	1	6	7	18	8	15

* Blood pressure not recorded in three cases.

† Blood urea nitrogen (BUN) not determined on admission in eleven cases.

‡ Condition 2, good; condition 3, seriously ill; condition 4, critically ill; arbitrary designations made usually by a second-year medical resident after examination in the C.G.H. admitting department.

§ Two cases: chronic osteomyelitis. One case each: acquired hemolytic anemia; cerebral hemorrhages unrelated to septicemia; bronchiectasis, severe; polycystic kidneys with uremia; bleeding duodenal ulcer and malignant lymphoma; pernicious anemia.

‖ More than one serious disease in eleven patients.

before 1948 in patients with bacterial endocarditis was 87 per cent and since 1948, 60 per cent.

In evaluating the results of treatment, however, the influence on the mortality rate of factors other than antimicrobial therapy must be considered before a fair estimate of the efficacy of treatment with drugs can be made. Age, for example, has been shown [*11,12*] to be an important factor in the outcome in staphylococcal septicemia. Table II lists several factors which were present in our patients. While some differences between groups are slight, it is apparent that the patients who died were an older and sicker lot on admission than the patients who survived. This must be borne in mind when scrutinizing the results of chemotherapy.

ANALYSIS OF TREATMENT RESULTING IN SUCCESS

Sixteen patients (29 per cent) survived. The salient features of each case appear in Table III (Cases 1 to 16). Three specific observations flow from an analysis of this group.

1. Staphylococcal septicemia is not often controlled quickly or dramatically: Successful treatment usually requires prolonged, high-dose antibiotic chemotherapy, and even under these circumstances resolution of fever and toxemia is as a rule slow. With two exceptions no patient recovered with less than fifteen days of chemotherapy. Large amounts of drug were usually necessary for control of the disease, although in one instance (Case 2) recovery followed the injection of an average of only 61,000 units of

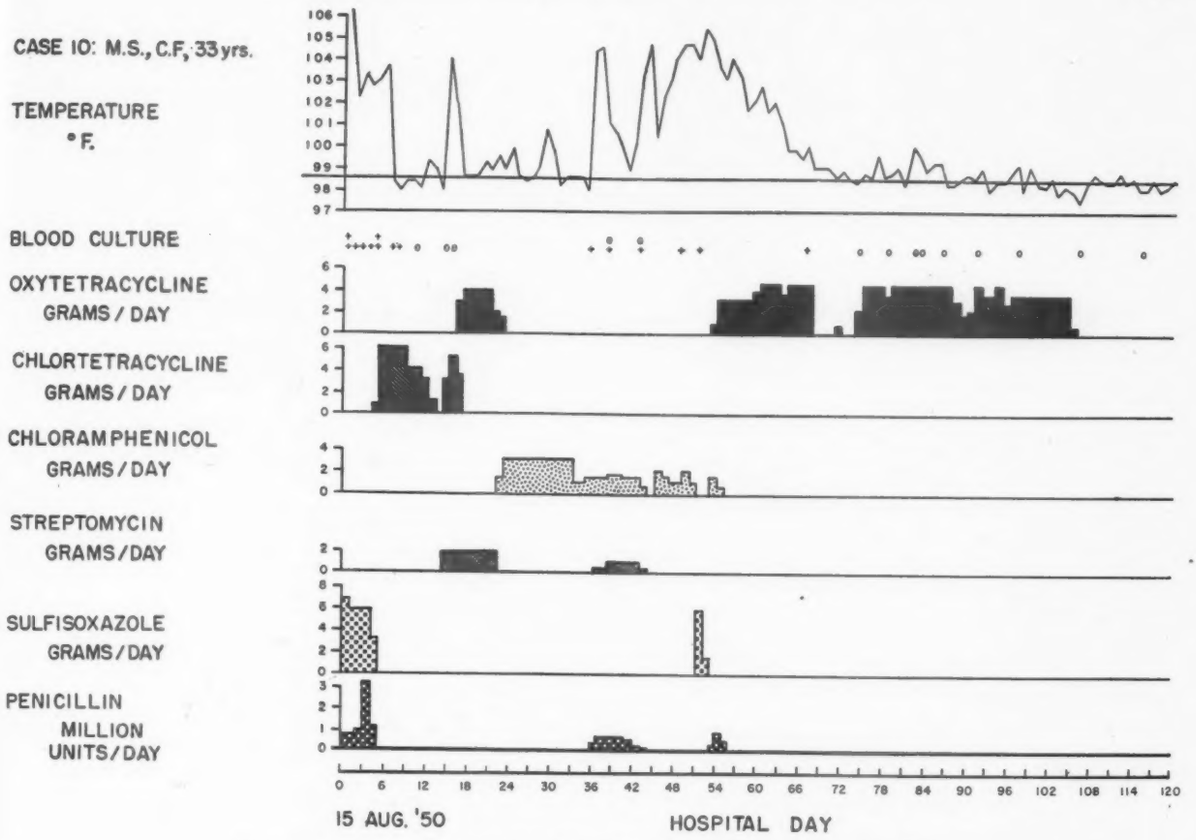

FIG. 1. Acute staphylococcal endocarditis. Response to oxytetracycline.

penicillin intravenously daily for twenty-six days. As an extreme example of the prolonged course of treatment which is often necessary to control staphylococcal septicemia the following case is presented. (Fig. 1.)

CASE 10. M. S. (No. 267115), a thirty-three year old Negro woman, was admitted in August, 1950, eleven days after an abortion, with a complaint of chills, pain, stiffness of the neck and vaginal bleeding. She had had "inflammatory rheumatism" four years previously.

On admission the patient was pale and severely ill. The temperature was 103.6°F., pulse rate 140 per minute, respiratory rate 18 per minute, blood pressure 124 systolic, 60 diastolic. The neck was stiff. There was a grade 2 apical systolic murmur which fluctuated in intensity throughout the hospital course. The uterus was enlarged and slightly tender.

Hemoglobin was 4.5 gm. per cent, white cell count 11,750 per cu. mm. Lumbar puncture was negative. Eight blood cultures were positive during the first week for hemolytic Staph. aureus. The organism was resistant to penicillin but sensitive to chlortetracycline, oxytetracycline and streptomycin.

During four months of hospitalization the patient was treated almost continuously with sulfisoxazole, penicillin, chlortetracycline, oxytetracycline, chloramphenicol and streptomycin, singly or in various combinations. Her course was characterized by repeated recrudescence of fever and malaise, an episode of severe uterine hemorrhage, calf vein thrombophlebitis, pulmonary infarction and signs of myocardial weakness, which may have been caused by abscesses of the myocardium. In addition it was thought that acute bacterial endocarditis was present. Blood culture relapse occurred on the thirty-fifth, thirty-eighth, forty-third, forty-ninth, fifty-first and sixty-seventh days but antibiotic sensitivity did not change except for development of moderate resistance to streptomycin. Cure was finally effected by the administration of large doses of oxytetracycline, much of it by jejunal tube, for forty-six days. Chlortetracycline and oxytetracycline had been given previously but had been discontinued because of severe nausea and vomiting. The patient was seen two years later at which time a heart murmur was not heard.

On the other hand, response is occasionally very rapid. (Fig. 2.)

CASE 8. P. K. (No. 256767), a nine year old white boy with an intraventricular septal defect and congenital aortic insufficiency, was admitted in

TABLE III

STAPHYLOCOCCAL SEPTICEMIA

SUMMARY OF CASES*

Case, Age, Race and Sex	Year	Underlying or Associated Disease	Endocarditis	Valves Infected	Meningitis or Cerebritis	Blood Culture	Minimum Inhibiting Concentration μg./ml.†	Chemotherapy		
								Drug‡	Average Daily Dose§	Days Given
1. J. M. 157698 18 W,M	1941	Furunculosis	+	Mitral(?)	0	Hemolytic Staph. aureus	.....	SD ST	4.0 6.6	18 5
2. P. S. 148071 39 N,M	1944	Infected abrasion; cirrhosis of liver(?)	0	.....	0	Hemolytic Staph. aureus	.....	PCN	0.061	26
3. H. D. 182713 15 N,F	1944	Chronic rheumatic heart disease; mitral insufficiency	+	Mitral(?)	0	Non-hemolytic Staph. aureus	.....	ST	8.4	30
4. J. H. 192625 58 W,M	1944	None	0	.....	0	Non-hemolytic Staph. aureus	.....	ST	7.0	3
5. W. C. 233647 40 N,M	1948	Alveolar abscesses(?)	0	.....	0	Hemolytic Staph. aureus	.....	PCN	0.30	8
6. W. H. 153598 36 W,M	1948	Infection, finger	0	.....	0	Hemolytic Staph. aureus	PCN 0.12	SD PCN	6.0 0.67	51 50
7. J. B. 254648 78 W,M	1949	Chronic rheumatic heart disease(?); mitral insufficiency(?)	+	Mitral(?)	0	Non-hemolytic Staph. aureus	PCN 0.015	PCN	0.80	42
8. P. K. 256767 9 W,M	1949	Interventricular septal defect	+	Septal defect(?)	+	Hemolytic Staph. aureus	PCN 0.06	SMZ PCN	3.75 1.1	8 31
9. T. Q. 257850 28 W,M	1950	Infected pilonidal cyst	+	Mitral	+	Hemolytic Staph. aureus	PCN 7.5 AMC 0.012 CMC >12.5 SM 0.08	SD PCN AMC CMC SM	3.4 2.4 6.3 4.0 1.3	55 49 26 44 51
10. M. S. 267115 33 N,F	1950	Chronic rheumatic heart disease; mitral insufficiency; septic abortion	+	Mitral(?)	0	Hemolytic Staph. aureus	1st week / 7th week PCN >7.5 / >7.5 AMC 0.1 / 0.2 TMC 0.49 / 0.49 SM <0.6 / 12.5	SFX PCN AMC TMC CMC SM	5.0 0.95 4.4 3.8 2.0 1.5	8 12 11 52 28 15
11. M. R. 291377 21 W,F	1951	Interventricular septal defect	+	Septal defect(?)	0	Staph. aureus	PCN 0.05	PCN	15.0	21
12. W. H. 286072 54 N,M	1952	Diabetes mellitus	0	.....	0	Staph. aureus	PCN 0.1 AMC 0.06 CMC 15.6 SM 1.0	SFX PCN AMC CMC SM	6.0 8.1 2.9 3.0 2.0	4 19 60 10 14
13. H. H. 297841 35 W,F	1953	Chronic rheumatic heart disease; mitral insufficiency; mitral stenosis; aortic stenosis	+	Mitral(?); aortic(?)	+	Hemolytic Staph. aureus	1st week / 4th week PCN >25.0 / >25.0 AMC 0.25 / 0.12 SM 31.2 / 31.2 EMC 1.56 / >50.0 BCN 1.2 / 1.2	PCN TCL SM EMC BCN	63.9 3.3 2.0 2.0 60.0	7 54 15 20 6
14. W. V. 300852 25 W,M	1953	None	+	Aortic	+	Staph. aureus	PCN >50.0 TCL <0.12 BCN 12.5	PCN TCL BCN	13.9 4.0 60.0	45 45 30
15. D. S. 299530 21 W,M	1953	Chronic rheumatic heart disease; mitral insufficiency; mitral stenosis	+	Mitral(?)	0	Hemolytic Staph. albus	PCN <0.012	PCN	15.0	15

* Patients 1 to 16 recovered; patients 17 to 55 died.

† Only results of tests of drugs used in treatment are listed. See Table IV for complete listing of *in vitro* tests.

‡ SD, sulfadiazine; SP, sulfapyridine; SPZ, sulfapyrazine; ST, sulfathiazole; SMZ, sulfamerazine; SFX, sulfisoxazole; PCN, penicillin G; TCL, tetracycline; AMC, chlortetracycline; TMC, oxytetracycline; CMC, chloramphenicol; SM, streptomycin; EMC, erythromycin; BCN, bacitracin.

§ Penicillin, millions of units; bacitracin, thousands of units; all other drugs, grams.

TABLE III (*Continued*)

STAPHYLOCOCCAL SEPTICEMIA

SUMMARY OF CASES*

Case, Age, Race and Sex	Year	Underlying or Associated Disease	Endocarditis	Valves Infected	Meningitis or Cerebritis	Blood Culture	Minimum Inhibiting Concentration μg./ml.†	Chemotherapy		
								Drug‡	Average Daily Dose§	Days Given
16. G. C. 310831 25 N,M	1954	Pancytopenia, unknown cause; corticotrophin and cortisone treatment; septic thrombophlebitis secondary to blood transfusion	0	.....	0	Staph. aureus	EMC 0.2 BCN 3.12	EMC BCN	1.1 100.0	56 12
17. E. H. 152886 45 W,M	1940	Cirrhosis of liver	0	.....	0	Staph. albus (postmortem)	.....	SP	7.0	1
18. C. H. 152856 21 W,M	1940	Chronic rheumatic heart disease; aortic stenosis; aortic insufficiency	+	Mitral(?); aortic(?)	0	Hemolytic Staph. aureus	.....	ST	13.0	1
19. M. G. 71344 70 W,F	1941	Cerebral thrombosis, mild	0	.....	0	Staph. aureus	.....	.....	None	..
20. R. F. 164322 49 W,M	1941	Chronic prostatitis; arteriosclerotic heart disease	0	.....	0	Staph. aureus	.....	SPZ	9.5	10
21. D. D. 168028 54 W,M	1942	Chronic rheumatic heart disease; aortic insufficiency	+	Aortic(?)	+	Staph. aureus	.....	ST	5.0	1
22. W. M. 172151 45 N,M	1942	Recurrent intracerebral hemorrhages	0	.....	0	Hemolytic Staph. aureus	.....	SD	7.0	4
23. E. S. 167933 34 W,M	1942	Chronic rheumatic heart disease; mitral insufficiency; infected burn	+	Mitral; aortic	0	Hemolytic Staph. albus	.....	.....	None	..
24. M. B. 24269 28 N,F	1942	Chronic rheumatic heart disease; mitral insufficiency; mitral stenosis, aortic insufficiency; aortic stenosis; tricuspid insufficiency	+	Mitral; aortic	+	Staph. aureus	.....	SD ST	7.0 3.7	5 7
25. H. M. 177792 67 W,M	1942	Chronic rheumatic heart disease; mitral stenosis; aortic stenosis	+	Mitral; aortic	+	Hemolytic Staph. aureus	.....	SD ST	5.0 5.0	1 1
26. M. M. 184079 61 W,F	1943	Chronic rheumatic heart disease; mitral stenosis; aortic stenosis; wound infection following open reduction and wiring of fracture, os calcis	+	Mitral; aortic	+	Staph. aureus	.....	SD ST PCN	7.5 3.6 0.01(?)	1 5 4
27. R. G. 186973 51 N,M	1943	Alveolar abscesses; arteriosclerotic heart disease; congestive heart failure	+	Aortic	0	Hemolytic Staph aureus	.....	SD	5.7	4
28. C. D. 189042 59 W,M	1943	Chronic rheumatic heart disease; mitral insufficiency; mitral stenosis; arteriosclerotic heart disease; congestive heart failure	+	Mitral; left atrium	0	Hemolytic Staph. aureus	.....	ST	5.8	5
29. A. G. 54993 55 N,M	1944	Cirrhosis of liver	+	Tricuspid	+	Hemolytic Staph. aureus	.....	ST	10.4	33
30. R. H. 191351 75 W,F	1944	Bronchiectasis	0	.....	0	Non-hemolytic Staph. aureus	.....	ST	5.8	6
31. H. H. 192481 19 W,F	1944	Postpartum, 2 months; syphilis	+	Aortic	0	Hemolytic Staph. aureus	.....	.....	None	..

TABLE III (*Continued*)

STAPHYLOCOCCAL SEPTICEMIA

SUMMARY OF CASES*

Case, Age, Race and Sex	Year	Underlying or Associated Disease	Endocarditis	Valves Infected	Meningitis or Cerebritis	Blood Culture	Minimum Inhibiting Concentration μg./ml.†	Chemotherapy		
								Drug‡	Average Daily Dose§	Days Given
32. L. L. 198709 39 W,M	1944	Chronic rheumatic heart disease; mitral stenosis; aortic stenosis; chronic osteomyelitis, 22 years	+	Mitral; aortic	0	Hemolytic Staph. aureus	.....	PCN	0.15	9
33. B. W. 108888 20 N,F	1946	Septic abortion(?)	0	.....	0	Staph. aureus; Str. hemolyticus	PCN 15.0	SD PCN	5.6 0.26	8 8
34. M. T. 224710 70 N,M	1947	Chronic rheumatic heart disease; mitral insufficiency; congestive heart failure	+	Mitral	+	Staph. albus	.....	PCN	0.6	1
35. H. G. 227015 45 N,M	1947	Chronic rheumatic heart disease; mitral stenosis; chronic urethral stricture with infection	+	Mitral(?)	+	Hemolytic Staph. aureus	.....	ST PCN SM	4.7 0.76 2.6	3 14 7
36. S. B. 245687 16 W,F	1948	Chronic rheumatic heart disease; mitral insufficiency; mitral stenosis; acute cervicitis	+	Mitral	+	Hemolytic Staph. aureus	PCN 0.06	PCN	11.5	19
37. M. K. 250286 57 W,F	1949	Chronic abscess axilla, staphylococcal; polycystic kidneys with uremia	0	.....	0	Hemolytic Staph. aureus (postmortem)	.....	PCN	0.20	1
38. R. J. 258129 57 N,F	1949	Bleeding duodenal ulcer; malignant lymphoma, retroperitoneal; diabetes mellitus; arteriosclerotic heart disease	0	.....	0	Staph. aureus	.....	PCN	0.5	1
39. J. S. 11026 79 W,M	1950	Diabetes mellitus; hypertensive and arteriosclerotic heart disease	0	.....	0	Non-hemolytic Staph. aureus (postmortem)	.....	.....	None	..
40. J. C. 263248 29 N,M	1950	Chronic rheumatic heart disease; mitral insufficiency; mitral stenosis; aortic insufficiency; aortic stenosis	+	Mitral(?); aortic(?)	0	Hemolytic Staph. aureus	PCN 0.015	PCN	15.0	14
41. B. B. 264709 55 W,M	1950	Chronic rheumatic heart disease; mitral stenosis	+	Mitral	+	Hemolytic Staph. aureus	PCN 0.06 AMC 0.78 SM >5.0	SD PCN AMC SM	5.7 1.1 0.5 2.0	3 2 2 1
42. B. C. 268015 62 W,M	1950	Cirrhosis of liver; primary visceral amyloidosis, extensive	0	.....	+	Hemolytic Staph. aureus	PCN >7.5 AMC 0.1 SM 2.5	SFX PCN AMC SM	3.0 0.4 1.1 0.75	3 13 4 6
43. J. W. 271321 55 W,M	1951	Diabetes mellitus	+	Mitral	+	Hemolytic Staph. aureus	PCN >25.0 AMC 0.2 TMC 0.3	SFX/SD PCN AMC TMC	4.8 2.2 1.0 1.2	5 4 4 2
44. C. W. 271194 65 W,M	1951	Chronic osteomyelitis, humerus; cirrhosis of liver(?)	0	.....	0	Hemolytic Staph. aureus	PCN >50.0 AMC 12.5 SM 0.3	SFX PCN AMC SM	5.3 0.8 1.9 2.0	3 5 9 8
45. H. B. 272332 67 W,M	1951	None	+	Mitral; aortic	+	Non-hemolytic Staph. aureus	PCN 50.0 AMC <0.12	PCN AMC	0.9 1.1	6 12
46. F. B. 150108 58 N,M	1951	Diabetes mellitus; chronic urethral stricture with infection	0	.....	+	Non-hemolytic Staph. aureus	PCN >25.0 SM <1.25	SFX PCN SM	4.0 0.9 0.7	3 3 3

TABLE III (*Continued*)
STAPHYLOCOCCAL SEPTICEMIA
SUMMARY OF CASES*

Case, Age, Race and Sex	Year	Underlying or Associated Disease	Endocarditis	Valves Infected	Meningitis or Cerebritis	Blood Culture	Minimum Inhibiting Concentration μg./ml.†	Chemotherapy		
								Drug‡	Average Daily Dose§	Days Given
47. A. M. 277345 75 W,M	1951	Chronic rheumatic heart disease; mitral stenosis, aortic stenosis; benign prostatic hypertrophy with obstructive uropathy and infection	+	Aortic	+	Hemolytic Staph. aureus	.....	.....	None	..
48. A. H. 279135 75 W,M	1951	Pernicious anemia; arteriosclerotic heart disease	+	Mitral(?)	0	Hemolytic Staph. aureus	.....	SFX PCN AMC	6.2 0.5 1.5	5 17 7
49. J. I. 271854 79 W,M	1951	Suprapubic cystostomy; paravesical abscess; arteriosclerotic heart disease	+	Mitral	+	Hemolytic Staph. aureus	.....	PCN SM	1.4 1.5	2 2
50. W. R. 284478 21 W,M	1952	Chronic cor pulmonale secondary to recurrent pulmonary infarction	+	Aortic	+	Hemolytic Staph. aureus	PCN 0.39 SM 0.5	SD PCN SM	2.0 2.0 1.0	1 1 1
51. A. O. 197228 80 W,M	1952	Benign prostatic hypertrophy with obstructive uropathy and infection	0	.....	0	Hemolytic Staph. aureus	.....	PCN TMC SM	1.1 1.0 1.0	2 1 1
52. R. M. 299483 44 W,F	1953	Chronic rheumatic heart disease; mitral stenosis; aortic stenosis	+	Mitral; aortic	+	Non-hemolytic Staph. aureus; Str. non-hemolytic	1st week / 8th week PCN 0.78 / 0.78 AMC 0.1 / 31.2 CMC 3.9 / 1.0 SM .... / 125.0 BCN .... / 0.04	PCN TCL CMC SM BCN	12.8 4.0 3.75 2.0 60.0	42 56 37 6 30
53. A. W. 163698 46 W,F	1953	Syphilitic aortitis and aortic valvulitis	+	Left ventricle	0	Staph. aureus	.....	PCN TMC	0.75 0.8	4 3
54. H. R. 307551 54 W,M	1954	Diabetes mellitus with severe acidosis	0	.....	0	Staph. aureus	PCN <0.025 TCL 0.25 CMC 15.6 SM 0.5	PCN AMC CMC SM	5.5 2.0 1.8 1.8	12 6 6 7
55. W. E. 141672 44 N,M	1954	Chronic rheumatic heart disease; aortic insufficiency; congestive heart failure	+	Aortic(?)	0	Staph. albus	PCN 0.003 SM <0.12	PCN SM	14.8 2.0	20 10

October, 1949, violently ill with acute staphylococcal endocarditis.

Eight hours after the start of intramuscular penicillin the temperature fell from 105.6°F. to 98.6°F. and except for an occasional rise to slightly over 100°F. remained essentially normal throughout thirty-one days of chemotherapy with varying doses of penicillin and sulfamerazine.

Symptomatic improvement was almost as dramatic. The patient was virtually symptom-free three days after the onset of chemotherapy. He did well for about three years but at the present time, which is six years after discharge, he has advanced heart failure.

2. Recovery seldom occurs unless a drug capable of killing or suppressing the organism in vitro is administered: That this is true constitutes the best argument that this material affords for the use of *in vitro* sensitivity tests as a guide of chemotherapy. In no instance did massive doses of penicillin exert a curative effect when organisms resistant to penicillin were present.

In several instances pairs of drugs, each effective *in vitro*, which have been shown in certain laboratory situations [*13–16*] to be antagonistic in their action on staphylococci, were used. On such regimens some patients recovered, others died. The fact that recoveries occurred (for example, one individual (Case 9) received five drugs simultaneously for fifteen days and four simultaneously for twenty-eight days) suggests,

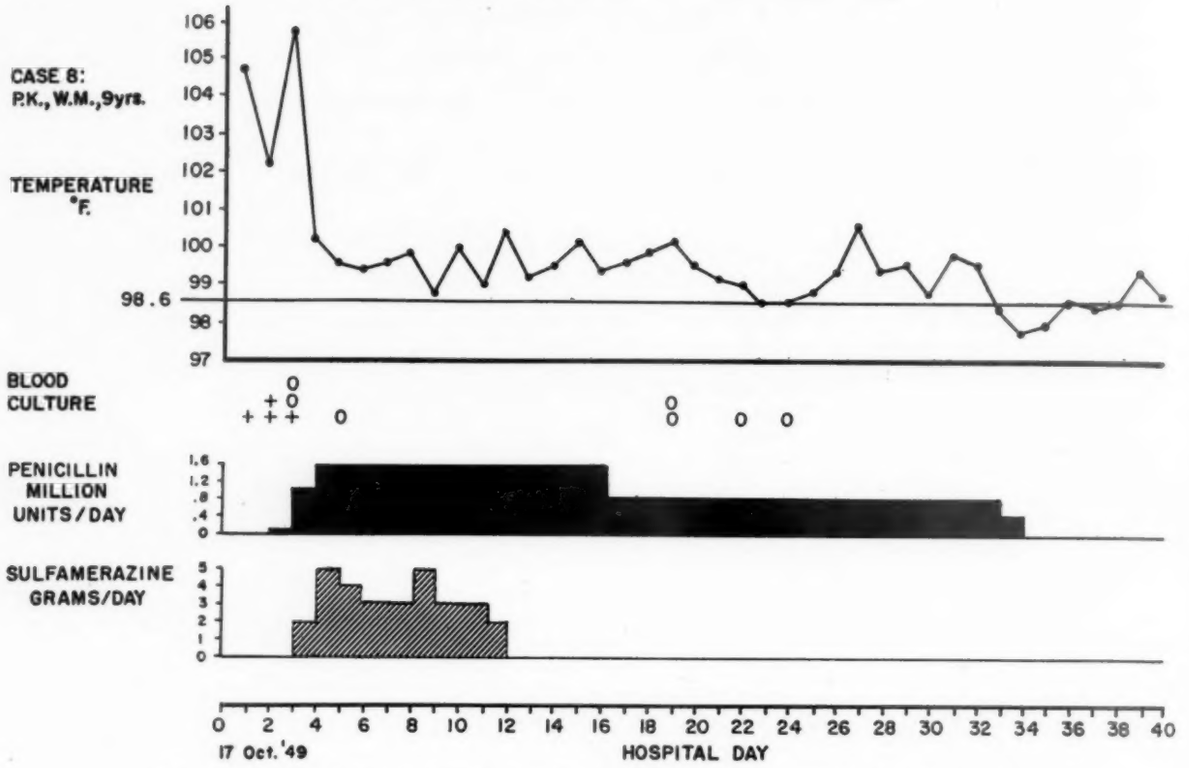

FIG. 2. Acute staphylococcal endocarditis. Treatment with penicillin and sulfamerazine.

as others have pointed out [7,8], that antibiotic antagonism is probably not a factor of major importance in the therapy of staphylococcus septicemia. Likewise the use of an agent ineffective *in vitro* in combination with a potent drug did not appear to lessen the effectiveness of the latter agent, although positive information concerning this is difficult to adduce.

It is interesting to note that success was achieved several times (Cases 10, 12 and 13) by the prolonged use of tetracycline-group agents, which ordinarily are presumed to be bacteriostatic rather than bactericidal.

3. Therapeutic measures in addition to correct chemotherapy are often needed for success: Obviously heart failure, diabetes mellitus, malnutrition and other concomitant problems must be controlled. Not always remembered, however, is the fact that surgical drainage of localized accessible collections of pus is mandatory if success is to be assured. This has been repeatedly emphasized by others [6,7,12,17–20]. In the following case the patient did not improve until a subdeltoid bursa abscess was drained.

CASE 12. W. H. (No. 286072), a fifty-four year old Negro, was admitted in July, 1952, with a complaint of pain in the flank, frequency of urination and thirst of one week's duration. He had been hospitalized three weeks previously for two weeks for what was interpreted to be acute pyelonephritis (organism unidentified) and diabetes mellitus.

On admission the patient was confused. Temperature was 104°F., pulse rate 140 per minute, respiratory rate 26 per minute, blood pressure 126 systolic, 80 diastolic. At no time during hospitalization was a heart murmur heard. There was tenderness in the right flank. Urinalysis showed sugar, acetone and numerous white blood cells, but culture was negative. Blood culture yielded Staph. aureus which *in vitro* was highly sensitive to penicillin, chlortetracycline and streptomycin.

The patient was given chlortetracycline, 2.0 gm. daily, but blood culture was again positive after 4.0 gm. had been administered. Cellulitis of the right shoulder and areas of purpura on the arm and trunk then appeared. Penicillin, 10 million units daily, sulfisoxazole, streptomycin, chloramphenicol and more chlortetracycline were then tried singly or in various combinations, but high fever continued and the shoulder swelling increased. Glycosuria was easily controlled with insulin.

Surgical drainage of the subdeltoid bursa abscess was performed on the forty-fourth hospital day. Following this and with the help of chlortetracycline, 3.0 gm. daily for forty-eight days, the fever subsided

quickly and permanently except for minor elevations associated with the instillation into the abscess cavity of streptokinase and streptodornase, which were also helpful in finally eradicating the cavity. The patient was discharged on the ninety-third hospital day and was well when seen six months later.

ANALYSIS OF TREATMENT RESULTING IN FAILURE

Thirty-nine patients (71 per cent) died. The salient features of each case appear in Table III (Cases 17 to 55). Twelve of these patients died before twenty-four hours of antibiotic chemotherapy could be given. A dismally high rate of death (49 per cent) prevails even when these twelve are excluded, and it demands analysis. Several reasons for failure of chemotherapy are apparent.

1. Chemotherapy may fail because of original resistance of the organism to the drug chosen: The following is an illustrative case.

CASE 33. B. W. (No. 108888), a twenty year old Negro woman, was admitted in September, 1946, desperately ill. History was incomplete. She had apparently had severe vaginal bleeding for several days.

The patient was delirious and dyspneic. The temperature was 106°F., pulse rate 130 per minute, respiratory rate 40 per minute, blood pressure 100 systolic, 50 diastolic. There were sibilant rales in the chest. The heart was not enlarged but there was a soft systolic murmur at the apex. Lower quadrant abdominal tenderness was found. The uterus was slightly enlarged and tender, and there was a bloody, purulent discharge from the cervix, which on culture yielded non-hemolytic streptococcus and Staph. aureus. Blood culture yielded Staph. aureus, resistant to greater than 15 μg. per ml. of penicillin and hemolytic streptococcus, highly sensitive to penicillin.

The patient was given approximately 32,000 units of penicillin every three hours for eight days together with sulfadiazine, 5.6 gm. daily. The streptococcus disappeared from the bloodstream but the staphylococcus did not; 471 colonies per ml. were present in the blood one day before death. The temperature remained between 102°F. and 106°F. Determination was progressive; the patient died on the ninth hospital day.

Autopsy disclosed acute endometritis, multiple small lung abscesses, lobular pneumonia and adrenal cortical necrosis. Bacterial endocarditis was not present. Staph. aureus was cultured from one of the lung abscesses.

Comment: In this case of mixed staphylococcus and streptococcus septicemia the small dosage of penicillin in vogue in 1946 was adequate to eradicate the streptococcal infection but was powerless against the penicillin-resistant staphylococcus.

2. Chemotherapy may fail because of acquired resistance of the organism: The case which follows of a thirty-five year old woman, who eventually recovered, illustrates this.

CASE 13. H. H. (No. 297841), a thirty-five year old white housewife, was admitted in July, 1953, with a complaint of malaise, chills, dyspnea and vomiting for three days. There was no history of rheumatic fever, but dyspnea on exertion and mild ankle edema had been present for two years, necessitating the use of digitalis.

The patient was severely ill. The temperature was 105°F., pulse rate 100 per minute, respiratory rate 22 per minute, blood pressure 90 systolic, 46 diastolic. The heart was slightly enlarged, with murmurs typical of aortic stenosis and mitral stenosis and insufficiency. Signs of heart failure were not present. Five blood cultures were positive for hemolytic Staph. aureus, which was highly resistant to penicillin but sensitive to chlortetracycline, erythromycin and bacitracin.

On the second hospital day penicillin therapy, 2.5 million units intramuscularly every four hours, was begun. One day later bacitracin, 10,000 units every four hours, and streptomycin, 1.0 gm. every twelve hours, were added to the regimen. On this program the blood culture remained positive, and on the fourth day stiff neck and confusion appeared. Lumbar puncture revealed 542 white blood cells per cu. mm., but culture was negative. Bacitracin, 10,000 units, was administered intrathecally daily for five days with improvement in the signs and symptoms of the meningitis.

On the fifth day the dosage of penicillin was increased to 80 million units daily but since there was no general improvement by the ninth day penicillin was abandoned, and erythromycin therapy, 0.5 gm. every six hours was begun; the streptomycin was continued. On this combination there was striking amelioration of symptoms. Fever subsided and blood cultures became negative.

Fever and malaise returned, however, on the twenty-first day and the blood culture again became positive, with increasing colony counts during the next few days. Whereas initially the organism had been inhibited *in vitro* by 1.56 μg. per ml. of erythromycin, retesting now showed resistance to greater than 50 μg. per ml. of this drug. Other *in vitro* values were essentially unchanged.

Erythromycin and streptomycin were discontinued and tetracycline therapy, 2.0 gm. daily, was begun on the twenty-third day. This was increased to 3.0 gm. daily on the twenty-ninth day and continued at a dose of 3 to 4 gm. daily for a total duration of tetracycline therapy of fifty-four days. Blood cultures remained negative after the twenty-fourth day and progressive improvement occurred. The patient is alive and active two and one-half years later but still takes digitalis.

Comment: This case illustrates acquired resistance to erythromycin which occurred despite the concomitant use of streptomycin. The case also illustrates successful management of early meningitis or cerebritis with bacitracin.

3. Chemotherapy may fail because of insufficient dosage of chemotherapeutic agents: The following case is illustrative.

CASE 43. J. W. (No. 271321), a fifty-five year old diabetic white man, was admitted in January, 1951, and died seven days later. He gave a history of cough, sweats, weakness and weight loss for one month and pain in the foot for five days.

The temperature was 104.8°F., pulse rate 120 per minute, respiratory rate 32 per minute, blood pressure 110 systolic, 85 diastolic. The heart was not enlarged and there were no murmurs. Swelling and tenderness were present on the dorsum of the right foot. Blood culture yielded hemolytic Staph. aureus, which was resistant *in vitro* to greater than 25.0 μg. per ml. of penicillin but sensitive to 0.2 μg. per ml. of chlortetracycline.

Chlortetracycline was given for four days but the total dose was only 4 gm. Penicillin in increasing amounts up to 1 million units every three hours was administered for four days, sulfisoxazole and sulfadiazine in moderately large doses for five days, and small amount of oxytetracycline during the last two days of the patient's life. Glycosuria was controlled with small amounts of insulin. Blood culture remained positive for Staph. aureus and deterioration was progressive; death occurred on the seventh day.

At autopsy an ulcer of acute endocarditis was found on an otherwise normal mitral valve. There was pyemic nephritis and septic infarction of the spleen and brain. Culture of the heart valve yielded Staph. aureus. Minimal inhibiting concentrations of antibiotics were almost identical with those of the original bloodstream organism.

Comment: In this case an average daily dose of 1.0 gm. of chlortetracycline was obviously inadequate to control infection in spite of sensitivity of the organism to the drug *in vitro*. Other drug therapy was equally indecisive.

4. Chemotherapy may fail despite "adequate" dosage of drugs: Patients may succumb to continuing infection despite the administration of large amounts of a chemotherapeutic agent demonstrated *in vitro* to be highly effective against the bloodstream organism. This occurred three times, once in a patient without bacterial endocarditis (Case 54) and twice in individuals with endocarditis:

CASE 36. S. B. (No. 245687), a sixteen year old white waitress, was admitted in December, 1948, with a history of malaise, joint aching and an intensely pruritic generalized urticaria of two weeks' duration following simultaneous upper respiratory and pelvic infections. At age six she had had acute rheumatic fever. There was no history of drug ingestion prior to admission.

The patient was severely ill. The temperature was 104°F., pulse rate 120 per minute, respiratory rate 30 per minute, blood pressure 90 systolic, 50 diastolic. There was widespread urticaria, most prominent on the limbs, and petechial hemorrhages beneath the fingernails. The fingertips were tender. The neck was not stiff. The chest was clear. The heart was extremely active and a murmur typical of mitral stenosis was present. The liver was moderately enlarged and the tip of the spleen was felt. There was acute cervicitis.

White blood cell count was 6,650 per cu. mm.; eosinophils 3 per cent. Sixty-eight white blood cells and 170 red blood cells were found in the otherwise normal cerebrospinal fluid. Five blood cultures were positive for hemolytic Staph. aureus which on testing was found to be sensitive to 0.1 μg. per ml. of penicillin.

Penicillin therapy, 100,000 units every three hours, was begun. The dose was increased to 2.5 million units every four hours, two days later, and continued for fifteen days. After an interruption of two days, penicillin was readministered at considerably lower dosage and continued until the patient's death. A total of 220 million units of penicillin was given. During the period of high dosage, serum levels of penicillin as high as 25.0 μg. per ml. one hour following a dose of 2.5 million units, and 12.5 μg. per ml. three hours following a similar dose were obtained.

Except for transient remission of fever, deterioration was progressive. In particular, marked tachycardia persisted and petechiae continued to appear, although blood culture was negative after the third day. Extensive lobular pneumonia finally supervened and the patient died on the twenty-second day.

At autopsy chronic rheumatic valvular heart disease with acute perforating bacterial endocarditis of the anterior leaf of the mitral valve was found. Microscopic section of the heart vegetation showed colonies of gram-positive cocci but culture of the vegetation was negative. Intense lobular pneumonia of all lobes of the lung was also present. Culture of the lung yielded hemolytic Staph. aureus. The brain and meninges were normal.

CASE 40. J. C. (No. 263248), a twenty-nine year old Negro laborer, was admitted in April, 1950, with a history of malaise, sweating and shortness of breath for two months. He had had four attacks of rheumatic fever in the past and had been rejected for military duty eight years previously because of the presence of heart murmurs.

The patient appeared seriously and chronically ill. The temperature was 97°F., pulse rate 96 per minute, respiratory rate 22 per minute, blood pressure 125 systolic, 60 diastolic. The lungs were clear. The

heart was greatly enlarged, and murmurs characteristic of aortic and mitral stenosis and insufficiency were present. The rhythm was regular. Signs of heart failure were not present. Daily blood culture for the first eight days of hospitalization yielded hemolytic Staph. aureus, sensitive to 0.015 μg. per ml. of penicillin. Low grade fever was present during the first week.

On the ninth day penicillin therapy, 2.5 million units every four hours, was begun and continued for fourteen days; a total of 210 million units was given. There was symptomatic improvement but complaints were not abolished. Following termination of the course of penicillin, symptoms of dyspnea, anorexia, abdominal fullness, nausea, occasional vomiting and great lassitude appeared, as did signs of congestive heart failure uncontrolled by the use of digitalis, diuretic agents and oxygen. Fever did not occur after the ninth day.

Blood cultures during and immediately following penicillin therapy were negative. Culture one day before death, however, yielded hemolytic Staph. aureus. The patient died on the forty-first hospital day, eighteen days after completion of the two-week course of penicillin. Autopsy was not performed.

Comment: Here, then, are two examples of infection with staphylococcus organisms highly sensitive *in vitro* to penicillin but not yielding in one instance to 220 million units given in twenty-two days and in another instance to 210 million units administered in a fourteen-day period. It is improbable that longer therapy could have saved the first patient inasmuch as progressive worsening occurred on high-dose therapy. It is distinctly possible, however, that earlier and longer treatment might have salvaged the second patient from his less violent infection, and that the doses of drug referred to as "adequate" were indeed not adequate at all in terms of duration of administration.

Four reasons have been presented, then, for specific failure of drug therapy to eradicate systemic staphylococcal infection. In addition to these, other clinical situations may contribute to failure. Factors such as (1) delay in diagnosis, (2) delay in onset of chemotherapy, (3) failure to ingest prescribed oral medication because of stupor, vomiting and the like, (4) failure to drain accessible abscesses, and (5) failure to control heart failure, uremia, diabetes mellitus, malnutrition and other conditions, can patently influence outcome. Some of these points have been touched upon already; others will be elaborated later.

IN VITRO SENSITIVITY TO ANTIBIOTICS OF STAPHYLOCOCCI RECOVERED IN THIS SERIES

Table IV presents all the *in vitro* antibiotic sensitivity tests performed on staphylococci recovered from the blood of our patients. A two-fold serial dilution test in broth was employed [*21*]. As others have noted [*22–24*], there is generally a sharp division between sensitivity on one hand and resistance on the other hand. This is especially true with regard to penicillin and chlortetracycline. In our cases the staphylococcus was either sensitive to less than 0.8 μg. per ml. of penicillin (and usually to less than 0.2 μg. per ml.) or was resistant to more than 7.5 μg. per ml. Similarly with chlortetracycline there was sensitivity to less than 0.8 μg. per ml. or resistance to 12.5 μg. per ml., 31.2 μg. per ml. and 62.5 μg. per ml., respectively, in the three cases which were found to be resistant in the series. Instances of resistance acquired during therapy with chlortetracycline (Case 52) and erythromycin (Case 13) were recorded. A single strain resistant to chloramphenicol has been encountered (Case 16). Finally it will be noted, as is the experience of others [*9,25–27*], that strains of staphylococci highly sensitive to penicillin still occur with considerable frequency.

MISCELLANEOUS CLINICAL ASPECTS OF STAPHYLOCOCCAL SEPTICEMIA

Turning to an analysis of several clinical aspects of staphylococcal septicemia, let us consider the following: (1) bacterial endocarditis, (2) intracranial infection, (3) skin and mucous membrane manifestations, and (4) admission diagnosis.

Bacterial Endocarditis. In the series of fifty-five cases, bacterial endocarditis was demonstrated at autopsy nineteen times. The types of heart disease and valves involved in these cases are shown in Table V.

The difficulties in diagnosing endocarditis during life have been recently re-emphasized [*9*]. Nevertheless we believe that clinical evidence justified the diagnosis of bacterial endocarditis in sixteen additional cases. In these, ten patients recovered and six died but were not autopsied. In each case there was strong evidence of valvular or congenital heart disease: ten patients had chronic rheumatic valvular disease, usually advanced; two had interventricular septal defect; two had changing murmurs with signs of progressive valve destruction; and two had loud systolic murmurs of uncertain derivation. In every instance of staphylococcal septicemia in which significant valvular heart disease was demonstrated at necropsy, bacterial endocarditis was also found. We are certain, therefore,

TABLE IV

STAPHYLOCOCCAL SEPTICEMIA

IN VITRO ANTIBIOTIC SENSITIVITY TESTS* OF BLOODSTREAM ORGANISMS

Case	Year	Penicillin (μg./ml.)	Tetracycline (μg./mg.)	Chlortetracycline (μg./ml.)	Oxytetracycline (μg./ml.)	Chloramphenicol (μg./ml.)	Streptomycin (μg./ml.)	Erythromycin (μg./ml.)	Bacitracin (units/ml.)	Neomycin (μg./ml.)	Remarks
6	1948	0.12	.....	.....	.....	.....	0.3	.....	.....	.....	.....
7	1949	0.015	.....	0.1	0.08	.....	.....	.....	.....	.....	.....
8	1949	0.06	.....	0.1	.....	.....	.....	.....	.....	.....	.....
9	1950	7.5	.....	0.012	1.0	>12.5	0.08	.....	0.78	12.5	.....
10	1950	>7.5	.....	0.1	0.49	.....	<0.6	.....	.....	.....	1st week
		>7.5	.....	0.2	0.49	.....	12.5	.....	.....	.....	7th week
11	1952	0.05	<0.12	0.5	<0.12	15.6	0.25	0.39	0.78	<0.12	.....
12	1952	0.1	.....	0.06	1.0	15.6	1.0	.....	7.8	.....	.....
13	1953	>25.0	0.25	0.25	0.25	15.6	31.2	1.56	1.2	2.0	1st week
		>25.0	.....	0.12	.....	7.8	31.2	>50.0	1.2	.....	4th week
14	1953	>50.0	<0.12	<0.12	0.25	7.8	0.5	0.78	12.5	2.0	.....
15	1953	<0.012	<0.12	0.25	<0.12	7.8	<0.12	0.1	1.56	<0.12	.....
16	1954	>25.0	>125.0	62.5	>125.0	125.0	>125.0	0.2	3.12	3.9	.....
33	1946	>15.0	.....	.....	.....	.....	0.78	.....	.....	.....	.....
36	1948	0.06	.....	0.2	0.5	>12.5	0.31	.....	0.78	3.12	.....
40	1950	0.015	0.25	0.1	0.5	6.25	0.078	1.56	0.5	0.39	.....
41	1950	0.06	.....	0.78	.....	.....	>5.0	.....	.....	.....	.....
42	1950	>7.5	.....	0.1	0.97	>6.25	2.5	.....	.....	.....	.....
43	1951	>25.0	.....	0.2	0.3	.....	1.25	.....	.....	.....	1st week
		>25.0	.....	0.1	0.6	.....	0.62	.....	.....	.....	2nd week valve culture
44	1951	>50.0	.....	12.5	77.4	.....	0.3	.....	.....	.....	.....
45	1951	50.0	.....	<0.12	5.0	>6.25	<1.25	.....	.....	.....	.....
46	1951	>25.0	<0.12	<0.12	0.78	>6.25	<1.25	0.39	3.12	2.0	.....
50	1952	0.39	0.25	0.12	0.5	7.8	0.5	0.39	6.25	1.0	.....
52	1953	0.78	.....	0.1	.....	3.9	.....	0.4	.....	.....	1st week
		0.78	125.0	31.2	62.5	1.0	125.0	0.2	0.04	<0.12	8th week
54	1954	<0.025	0.25	<0.12	0.25	15.6	0.5	0.78	12.5	2.0	.....
55	1954	0.003	0.07	<0.12	<0.12	2.0	<0.12	0.05	1.56	<0.12	.....

* Two-fold serial dilution test in broth [*21*].

that in most of the sixteen unproved cases the patients did, indeed, have endocarditis. The total number of patients with proved or probable endocarditis, then, was thirty-five or 64 per cent of the entire series.

With regard to the twenty remaining patients, eleven were proved by autopsy not to have bacterial endocarditis. Several of these had, during life, soft systolic murmurs and one (Case 38) had a harsh systolic and a soft diastolic murmur at the base attributable at autopsy to arteriosclerosis of the aorta and aortic valve. It is impossible to be certain about the other nine patients, six of whom recovered. One (Case 16) had a soft apical systolic murmur, eight had no murmur. But this does not exclude the possibility that endocarditis was present, for three of the six autopsied subjects with endocarditis which occurred in normal hearts or in hearts with non-valvular disease did not have any murmur, while a fourth exhibited only a faint apical systolic murmur. An example is Case 43 already presented.

Fortunately, most patients who survive staphylococcal septicemia do so without major residua. This makes achievement of cure particularly gratifying. Sequelae are relatively uncommon even when bacterial endocarditis has been a part of the disease, and it is both surprising and pleasing to observe how little alteration from previous symptomatology a patient with underlying chronic heart disease may display

after recovering from staphylococcal endocarditis. Case 13, already cited, in which the patient survived acute endocarditis and meningitis, exemplifies this. On the other hand major damage due to the infection sometimes occurs.

TABLE V
STAPHYLOCOCCAL ENDOCARDITIS
PATHOLOGIC FINDINGS IN
NINETEEN CASES

Type of heart disease and valve involved:		
Chronic rheumatic		11
Mitral and aortic valves	6	
Mitral valve only	3	
Mitral valve and left atrium	1	
Aortic valve only	1	
Syphilitic		2
Aortic valve	1	
Left ventricle	1	
Arteriosclerotic		2
Mitral valve	1	
Aortic valve	1	
Chronic cor pulmonale		1
Aortic valve	1	
Normal heart		3
Mitral valve	1	
Mitral and aortic valves	1	
Tricuspid valve	1	
Totals		19

CASE 14. W. V. (No. 300852), a twenty-five year old white man, was admitted in November, 1953, with acute staphylococcal septicemia. On the admission examination the heart was normal except for a faint apical systolic murmur, but a murmur of aortic insufficiency appeared during the second week and became progressively louder. The bloodstream organism was resistant to penicillin but sensitive to tetracycline. The patient was treated for fifty-one days with varying combinations of penicillin, tetracycline and bacitracin, and gradually improved. Mild meningitis was present on admission but cleared rapidly. Two years later the physical signs of aortic insufficiency remain but the patient does not consider himself handicapped.

Comment: In this case staphylococcal endocarditis produced aortic insufficiency in a heart presumably normal prior to the infection but the degree of damage was not great enough to disable the patient.

One other case of endocarditis deserves detailed presentation, for recurrence or reactivation of infection occurred four years after the initial bout of acute endocarditis.

CASE 9. T. Q. (No. 257850), a twenty-eight year old white man, was admitted in January 1950, with a five day history of malaise, chilliness, headache, vomiting and finally delirium. Two months prior to admission he had had the second of two operations for removal of a pilonidal cyst. Previously health had been excellent.

The patient was irrational and desperately ill. The temperature was 102.6°F., pulse rate 140 per minute, respiratory rate 40 per minute, blood pressure 140 systolic, 80 diastolic. There were numerous petechiae on the trunk, extremities and palate, along with several areas of purpura. The neck was stiff. The heart and lungs appeared to be normal on admission but on the second day a soft apical systolic murmur appeared and within several days became harsh and grade 4 in intensity. There was a small granulating area over the coccyx which on culture yielded a pure growth of hemolytic Staph. aureus.

The white blood cell count was 13,100 per cu. mm. with 91 per cent neutrophils. Lumbar puncture showed cloudy fluid with 108 white blood cells, 90 per cent neutrophils; protein 205 mg. per cent; sugar 109 mg. per cent; culture yielded hemolytic Staph. aureus. Three blood cultures during the first five days of hospitalization were positive for hemolytic Staph. aureus resistant to 7.5 μg. per ml. of penicillin but sensitive to 0.012 μg. per ml. of chlortetracycline and to 0.08 μg. per ml. of streptomycin.

The patient was treated for fifty-five days with large doses of penicillin, chlortetracycline, streptomycin, chloramphenicol and sulfadiazine in varying combinations. For a fifteen-day period he received five drugs concurrently, for twenty-eight days four drugs concurrently, and at other times he received at least three drugs simultaneously.

On this intensive program the patient gradually improved. Specific credit could not be given to any single drug or combination of drugs although gradual lysis of the fever occurred only after chloramphenicol was added on the twelfth day. The petechial hemorrhages faded rapidly although a few new ones appeared as late as the fourth week. The signs and symptoms of meningitis subsided within one week. The heart murmur remained loud but signs of failure did not develop despite considerable tachycardia which persisted until about two weeks before discharge on the seventy-fifth hospital day. Six months later the systolic murmur had decreased to grade 2 intensity.

The patient remained well for four years but was then admitted to another hospital with a sudden subarachnoid hemorrhage and died four weeks later. Blood culture was negative but autopsy* showed both firm, grayish white "healed" vegetations and a single pinkish red "recent" vegetation on the anterior leaflet of the mitral valve. Gram-positive cocci were visible in stained sections of the recent vegetation. In the anterior wall of the left ventricle directly beneath the anterior leaflet of the mitral valve there was an intramural aneurysm, 2 by 2.5 cm. in size, thinning the left ventricular wall to a thickness of about 1 mm. The

* Information furnished by Dr. Frank P. Cleveland.

wall of the aneurysm was lined with thick, gray endocardium and contained no clot. In addition there were multiple old mycotic aneurysms of the circle of Willis, the rupture of one of which caused death. It was the impression of the pathologist that the cardiac and intracranial aneurysms were produced at the time of the staphylococcal septicemia in 1950 by the extension of endocardial and intimal infection respectively into muscle layers.

Comment: In this case the infectious process had undoubtedly been arrested originally but leakage from one of the cerebral aneurysms four years later was fatal. It is impossible to say whether or not the acute bacterial endocarditis found at autopsy represented reinfection or reactivation of old infection.

It is important to note, finally, that the presence of bacterial endocarditis in staphylococcal septicemia did not appear in this series to have decreased the chance for survival under treatment. Ten of thirty-five patients (29 per cent) with proved or reasonably certain endocarditis recovered and, if the eight individuals who did not receive at least twenty-four hours of chemotherapy are excluded, ten of twenty-seven (37 per cent) survived. Of twenty patients without endocarditis six (30 per cent) recovered and again, if those who received less than twenty-four hours of treatment are excluded, six of sixteen (38 per cent) survived. The two groups, then, with endocarditis or without endocarditis, fared the same.

Four of the ten patients with endocarditis who recovered received thirty days or less of chemotherapy, while three of the six with septicemia but without evidence of endocarditis recovered after twenty-six days or less of drug therapy. Because of the relatively few recoveries in each group, however, no conclusion can be drawn concerning the amount or duration of chemotherapy necessary to eradicate staphylococcus septicemia with or without endocarditis.

Intracranial Infection. It has long been recognized that the cerebral complications of systemic staphylococcal infections are common [*20,28–33*]. Twenty-one patients in this series exhibited evidence of cerebral involvement, an incidence of 38 per cent. Bacterial endocarditis was present in all but two of twenty-one cases. The incidence of spread of infection to the brain or meninges was five times as great in patients with endocarditis (54 per cent) as when the heart valves were not infected (10 per cent).

Clinically most of the patients with meningitis or cerebritis were stuporous or comatose and the majority exhibited nuchal rigidity. Convulsive seizures, either generalized or focal, were uncommon but hemiparesis and various other neurologic signs were not unusual.

In the cerebrospinal fluid the changes were variable. The findings are summarized in Table VI. As many as 1,000 white blood cells per cu. mm., mostly polymorphonuclear leukocytes, were present but lower counts were more usual. Leakage of red blood cells into the subarachnoid space was common but massive bleeding was not. Cerebrospinal fluid protein was often elevated, however high values and cerebrospinal fluid block have not been observed. Staphylococci were not often discovered on smear or culture of the fluid—a positive smear twice and a positive culture three times among four individuals—but it must be remembered that chemotherapy had often been in progress for several hours or days prior to lumbar puncture. The cerebrospinal fluid sugar was not significantly depressed even in fluids in which smear or culture was positive for the staphylococcus.

TABLE VI
STAPHYLOCOCCAL MENINGITIS AND CEREBRITIS
SUMMARY OF CEREBROSPINAL FLUID FINDINGS
IN TWENTY CASES

	Range*	Median
Pressure, mm. H_2O (15 cases)	120–480	180
White blood cells (20 cases)		
Total	0–1000	110
Neutrophils %	0–100	83
Red blood cells (13 cases)	0–9520	70
Protein, mg. % (17 cases)	20–205	52
Sugar† mg. % (12 cases)	38–132	62
Smear (11 cases)		
Positive	2	...
Negative	9	...
Culture (17 cases)		
Positive	3	...
Negative	14	...

* Most abnormal value in each case used in compilation.

† Patients receiving intravenous glucose or with diabetes mellitus excluded.

Upon gross postmortem examination brains from patients who died with staphylococcal septicemia complicated by meningitis or cerebritis often presented only mild edema, softening, and occasionally a few petechial hemorrhages. When examined microscopically, however, characteristic findings were widespread occlusion of

small blood vessels with bits of infected thrombus. (Table VII.) Clumps of cocci were sometimes visible within the occluded vessel. An intense polymorphonuclear leukocyte reaction was usually seen in and around the vessel, with infarction, liquefaction and miliary abscess formation

TABLE VII
STAPHYLOCOCCAL SEPTICEMIA; MENINGITIS AND CEREBRITIS
PATHOLOGIC FINDINGS IN NINE CASES

Case	Pathologic Findings
24	Diffuse purulent leptomeningitis; multiple septic brain emboli with infarction; miliary brain abscesses
25	Early acute leptomeningitis; large cerebral hemorrhage, parietal lobe; miliary septic brain infarct and abscesses
26	Meninges normal; multiple septic emboli in brain with miliary abscesses; numerous infectious granulomas of brain
34	Meninges normal; numerous foci of anemic and hemorrhagic infarction with areas of miliary abscess formation; many small vessels plugged with emboli composed of white blood cells and clumps of gram-positive cocci
41	Meninges normal; a few petechiae in white matter
43	Meninges normal; one and one-half centimeter septic infarct, occipital lobe
45	Focal encephalitis, acute, right parietal and occipital lobes, secondary to septic emboli, with early miliary abscess formation; one centimeter abscess occipital lobe
47	Early acute leptomeningitis; brain otherwise normal
49	Early acute leptomeningitis; brain otherwise normal

in the adjacent brain substance. Such microabscesses were frequently extremely numerous and widely distributed throughout the brain. Changes similar to these have been described by others [*28,29,34–48*].

Larger areas of infarction and abscess occurred, too, but were distinctly less common than were small lesions. In one instance a 1.5 cm. septic infarct of the occipital lobe was found and represented the only lesion of any consequence found in the brain. In another case a 1.0 cm. abscess was discovered, again in the occipital lobe, along with smaller more typical lesions scattered widely throughout the brain.

The meninges were apparently involved in either of two ways: (1) by direct blood-borne implantation or (2) by spread of infection from infarcted brain. Meningitis appeared to be distinctly less important in its effect upon the patient than cerebral infarction and abscess. Frank meningitis with grossly purulent spinal fluid was not generally seen. Rather, meningeal reaction appeared in most instances to be secondary to the underlying brain disorder.

TABLE VIII
STAPHYLOCOCCAL SEPTICEMIA
SKIN AND MUCOUS MEMBRANE MANIFESTATIONS
IN FIFTY-FIVE CASES

Number of patients with lesions	30
Petechial hemorrhages	16
Purpura	9
Pustules	3
Osler's nodes	3
Subcutaneous abscess	3
Urticaria, generalized	1
Erythema multiforme	1
Associated bacterial endocarditis	21
Number of patients without lesions	25
Associated bacterial endocarditis	14

Despite the high mortality rate (81 per cent) among patients with intracranial involvement, it was often surprisingly easy to abolish the manifestations of meningitis and cerebritis with vigorous antibiotic chemotherapy, using penicillin alone or combinations of various drugs. A total of eight patients (Cases 8, 9, 13, 14, 35, 42, 43, 52) were successfully managed in this manner but four (Cases 35, 42, 43, 52) of the eight died soon afterwards of other effects of the septicemia; a fifth (Case 9) died several years later of rupture of an old mycotic aneurysm of the brain. In only two instances was intrathecal chemotherapy used—penicillin in Case 35, in which the patient died, and bacitracin in Case 13, in which the patient recovered.

We therefore do not consider meningitis and cerebritis to be uniformly dire complications of staphylococcal septicemia, for it is probable that even widespread miliary infarction and abscess formation can occasionally be eradicated by vigorous systemic antibiotic chemotherapy. Complicated diagnostic maneuvers to identify lesions large enough to be assaulted neurosurgically are probably not warranted as a rule inasmuch as miliary lesions usually predominate.

Skin and Mucous Membrane Manifestations. The cutaneous, subcutaneous and mucosal display of staphylococcal septicemia is extremely variable. Thirty individuals (55 per cent) had skin lesions, twenty-five (45 per cent) did not. The findings are presented in Table VIII.

In only three instances were the skin lesions definitely pustular, as has been described as pathognonomic [*39*] of staphylococcal septicemia; but when pustular petechiae, pustular purpura or subcutaneous abscesses occur, staphylococcal origin is strongly suggested.

The most typical manifestation in the skin was the petechial hemorrhage, varying from one to ten lesions in some cases to dozens of lesions in the occasional case. These lesions were indistinguishable in size and configuration from the petechiae which are seen in Str. viridans endocarditis, and it is of more than passing interest that bacterial endocarditis was present in fifteen of the sixteen patients exhibiting petechial hemorrhages. The single exception was a patient without endocarditis in whom petechiae appeared later in the course of the illness and may have been related to excessive dosage of sulfapyrazine (Case 20).

Purpura varying from one or two areas of ecchymosis to florid skin hemorrhage was observed in nine patients. Five had endocarditis; four did not. In only one instance was accompanying thrombocytopenia of significant degree found (Case 53).

Less frequent skin manifestations included Osler's nodes (three cases), subcutaneous abscesses (three cases), generalized urticaria (one case) and erythema multiforme (biopsy diagnosis) manifested by a macular eruption, bullae, crusted lesions in the mouth and gangrene of the tips of the toes (one case).

Combinations of lesions, such as petechiae and ecchymoses, were present in several individuals.

Admission Diagnosis. Staphylococcus septicemia is particularly treacherous because it usually produces no telltale symptoms or signs. The onset may be insidious or it may be explosive. The course may be protracted and mild or the patient may die violently within a few days [*40–48*]. There is no characteristic rash. There is no typical pattern of fever. Virtually any system of the body may be involved. In this series septicemia or endocarditis was suspected on admission only sixteen times (29 per cent).

To illustrate these difficulties, admission diagnoses are listed in Table IX. Initial examination and diagnosis in almost every instance was made in the Cincinnati General Hospital admitting ward by a second-year medical resident and thus represents the opinion of someone with more than minimal diagnostic ability. The amazing variability in the initial diagnosis, which was often echoed through the first few days of hospitalization by interns, other residents and staff consultants, is apparent. The fact that blood culture was obtained during life in all but three patients indicates, however, that the possibility of septicemia came to mind. Positive diagnosis can be established during life in only one way—by blood culture.

TABLE IX
STAPHYLOCOCCAL SEPTICEMIA
ADMISSION DIAGNOSIS IN FIFTY-FIVE CASES

Septicemia suspected	16
Admission diagnosis	
Subacute bacterial endocarditis	11
Acute bacterial endocarditis	3
Septicemia (without endocarditis)	2
Septicemia not suspected	39
Admission diagnosis	
Pneumonia	9
Heart failure, uncomplicated	4
Pyelonephritis, acute	3
Fever of undetermined origin	3
Gonorrheal arthritis, acute	2
Meningitis, acute	2
Cirrhosis of liver, uncomplicated	2
Diabetes acidosis, uncomplicated	2
Rheumatic fever, acute	1
Miliary tuberculosis	1
Typhoid fever	1
Poliomyelitis, acute	1
Neurosyphilis, active	1
Osteomyelitis, acute and chronic	1
Infected compound fracture of foot	1
Cellulitis, pelvic, secondary to rupture of urethra	1
Urinary retention, acute, secondary to urethral strictures	1
Thrombophlebitis, saphenous, acute	1
Hemolytic anemia, acute, cause undetermined	1
Anemia, cause undetermined	1
Total	55

In spite of the infrequency of early accurate diagnosis there was no overall gross difference between the group who survived and the group who died, with respect to the following factors: (1) time of initial blood culture, (2) time of receipt on the hospital ward of the report of the initial positive blood culture, (3) onset of empiric chemotherapy, and (4) onset of "correct" chemotherapy as judged by *in vitro* sensitivity studies. This lack of difference may be related to the relatively small size of the series and the great number of variables involved in outcome. It is interesting, however, to find that

in many successfully treated patients "correct" chemotherapy was not begun until several days after admission. In one instance there was a delay in treatment of twenty-five days (Case 15); in another twenty-one days (Case 7). In patients with fulminating infection who survived, treatment was as a rule prompt and diligent, as earlier protocols and tables indicate.

COMMENTS

Staphylococcus septicemia continues to occur at a roughly constant yearly rate at the Cincinnati General Hospital. This is indication enough of the continuing seriousness of the problem, for the disease, even when recognized promptly and treated vigorously, has a high mortality rate.

Staphylococcus infection as a cause of endocarditis is second in frequency only to Str. viridans and is usually more difficult to treat than streptococcal endocarditis.

There is general agreement that the guidance afforded by careful *in vitro* antibiotic sensitivity tests of the blood stream organism is of tremendous value in the management of staphylococcal septicemia and endocarditis; but several other important questions regarding treatment, which experience has not yet definitively answered, remain.

1. What drug or drugs should be prescribed prior to receipt of the results of in vitro antibiotic sensitivity tests? No firm recommendation can be made regarding initial treatment. Most authorities advise the use of two drug agents, usually penicillin and a "broad-spectrum agent," in the hope that the infecting organism will be inhibited or killed by at least one of the agents or that an additive or synergistic effect will be achieved. Experience in the community with serious staphylococcal infections often suggests to the clinician which compounds to choose at the outset.

Dowling et al. [*49*] have suggested that a combination of erythromycin and chloramphenicol be employed initially. There is much to recommend this regimen on theoretic grounds for it has been demonstrated that when erythromycin and chloramphenicol are not used promiscuously the incidence of strains of Staph. aureus resistant to either agent is low [*24,50–53*]. Experience, however, has shown that erythromycin alone is not often effective in staphylococcal endocarditis because of the rapid development of resistance [*25,54–57*]; but there is considerable laboratory and some clinical evidence to show that when used in combination with another agent, such as penicillin or streptomycin, resistance does not appear so readily or so rapidly [*57–61*]. Our experience with the combination Dowling suggests is not extensive, being confined to a few patients treated since this compilation was made.

We have encountered few strains of staphylococcus resistant to chloramphenicol or drugs of the tetracycline group (Table IV) and accordingly have been inclined recently to use these agents in combination with penicillin or erythromycin as initial therapy, administering 2 to 4 gm. of chloramphenicol or tetracycline daily together with equal amounts of erythromycin or penicillin in dosage of at least 15 million units daily.

Streptomycin and bacitracin have less use, in our experience, but may be given to good advantage if they are effective *in vitro* when other drugs fail. Streptomycin should never be employed alone for, like erythromycin, resistance may develop rapidly [*22,23,49,61*]. Bacitracin, of course, should be used cautiously when renal impairment exists.

2. Should penicillin be a part of every regimen? Because no instance of cure using an agent as principal therapy which was ineffective *in vitro* has been observed by us, and because cure has been achieved in endocarditis without using penicillin, we see no reason to use penicillin if *in vitro* resistance has been established. Fisher et al. [*9*] advocate the use of penicillin even though high resistance is demonstrated but do not cite patients cured without the additional use of other agents effective *in vitro* against the organism. Geraci [*62*], however, has recorded one case of penicillin-resistance staphylococcal endocarditis in which the patient was cured with "massive" doses of penicillin.

3. Can so-called "bacteriostatic" agents cure staphylococcal endocarditis? Instances of cure of endocarditis with sulfonamides, tetracycline and oxytetracycline have been presented. Reports of cure of staphylococcal endocarditis by the use of a single bacteriostatic drug are, however, relatively few [*31,46,63–71*]. In general, the simultaneous use of two or more agents, effective *in vitro*, is recommended.

4. Does drug synergism occur in clinical practice? Is drug antagonism important clinically? No certain information concerning antibiotic synergism or antagonism can be culled from our cases. True synergism of antimicrobial agents has rarely

been convincingly demonstrated *in vivo* in staphylococcal infections [*69,72*]. We are in accord with Spink [*7*] in believing that antagonism between antibiotic agents is probably unimportant in the treatment of staphylococcal septicemia and do not hesitate to use combinations of drugs which in certain laboratory situations have exhibited antagonism in their action on staphylococci [*13–16*]. Other studies, it may be added, have demonstrated *in vitro* synergism against some strains of staphylococci of various combinations of certain so-called [*15*] "Group I" (penicillin, streptomycin and bacitracin) and "Group II" (chlortetracycline, oxytetracycline and chloramphenicol) agents [*73–76*]. For this reason and until definitive information as to antagonism in the range of drug dosage ordinarily used in serious infection is available, the simultaneous usage of any two or more of the commonly used drugs cannot be condemned.

5. What are the minimal amounts of various drugs necessary to cure staphylococcal septicemia? What are the optimum amounts? How long should therapy be continued? Most experienced physicians believe that a longer and higher dose treatment is requisite for the cure of staphylococcal endocarditis than for septicemia without endocarditis. Our data can neither support nor refute this opinion. The fact that staphylococcal endocarditis has been cured by as little as 4.6 gm. of sulfonamide daily for twenty-three days (Case 1) or by as little as 800,000 units of penicillin daily for forty-two days (Case 7) or by 15 million units of penicillin daily for fifteen days (Case 15) and twenty-one days (Case 11) suggests that either relatively brief, high dose therapy or prolonged moderate dose therapy can be effective in the presence of sensitive organisms. Until experience defines optimal dose and duration, however, it would seem wise, especially when treating endocarditis, to employ high doses of "correct" antimicrobial agents continuously for periods of not less than six weeks.

6. Should drugs shown to be effective in vitro be continued if blood culture relapse occurs on high dosage of the agent? Clinical and bacteriologic relapse during the treatment of typhoid fever, brucellosis and tuberculosis is not uncommon and does not necessarily indicate that the drug regimen originally selected will not eventually effect cure. Similarly with staphylococcal infections increasing experience leads us to believe that blood culture relapse does not necessarily spell defeat for a drug regimen unless the organism has developed resistance to the drug or drugs employed. In many instances the recrudescent organism grows only slowly in blood culture, suggesting that some inhibition by the drug continues to occur in the culture flask. We believe in such circumstances the agent should be continued if it is still potent *in vitro* and have witnessed ultimate eradication of disease by such agents even after temporary blood culture relapse (Case 10). This has also been the experience of others [*9,67,71,77*].

The management of this treacherous disorder, therefore, continues to be one of the most challenging problems in the field of antibiotic therapy today, as Spink has emphasized [*7*]. More questions concerning therapy remain to be answered than have been answered. It is indeed unusual, especially in the realm of infectious diseases, that no "recommended therapy" can be confidently advanced. Success depends not upon a formula to be applied to every case but upon a series of judicious decisions based initially on knowledge of the experience in the community with staphylococcal infections and later upon *in vitro* antibiotic sensitivity tests, together with vigilant insistence that high-dose medication is actually received, evacuation of accessible pus, and careful management of collateral medical problems. Such a program taxes the ingenuity and patience of the physician, nurse, laboratory technician and patient alike, but cure cannot be wrought without it and lamentably often cannot be achieved with it.

SUMMARY AND CONCLUSIONS

Since 1940, fifty-five cases of staphylococcal septicemia have been observed at the Cincinnati General Hospital. Thirty-five patients (64 per cent) had bacterial endocarditis.

The mortality rate prior to 1948 was 83 per cent, since 1948 it has been 62 per cent. Fatalities among patients with endocarditis were no more frequent than among patients without this complication, the mortality rate prior to 1948 being 87 per cent and since 1948, 60 per cent.

Meningitis, cerebritis and petechial hemorrhages in the skin and mucous membranes occurred almost exclusively among patients with bacterial endocarditis and were rarely encountered in patients without endocarditis.

Successful management of staphylococcal septicemia is dependent upon prolonged, high-dose chemotherapy guided by *in vitro* testing of the offending organism for sensitivity to anti-

biotic agents, together with control of collateral medical problems in the patient.

No single drug regimen can be confidently recommended for use prior to *in vitro* testing of the blood stream organism but various combinations, in pairs, of penicillin, tetracycline, chloramphenicol and erythromycin are suggested. When antibiotic sensitivities are known, two or more of the drugs most effective *in vitro* should be administered continuously for at least six weeks.

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Scarlet Fever*

Results of a Controlled Study of 609 Patients Treated with Penicillin and Sulfisoxazole

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In recent years, the effectiveness of penicillin for the treatment of streptococcal infections has been reported by many investigators [*1–4*]. Pouche and Carletti [*5*] reported that hemolytic streptococci failed to grow in media containing 0.01 units of penicillin per cc. but did grow in media containing 25 mg. per cent of a mixture of sulfamerazine, sulfathiazole and sulfapyridine. These authors concluded that these *in vitro* studies confirmed the clinical findings that sulfonamide drugs are not as efficacious as penicillin in the treatment of scarlet fever. The effectiveness of penicillin in alleviating the symptoms of the patient and its ability to eradicate streptococci from the throat were reported by Denny, Wannamaker and Hahn [*6*]. Massel et al. [*7*] were of the opinion that rheumatic fever recurrences could be reduced by the prompt use of penicillin, if continued for ten days. Their findings support the studies of other investigators who report that the incidence of initial attacks of rheumatic fever can be reduced by penicillin therapy of clinical streptococcal infections. On the other hand, Weinstein, Bachrach and Boyer [*8*] have indicated that penicillin does not prevent rheumatic fever or glomerulonephritis, and the use of penicillin in the treatment of streptococcal pharyngitis does not eliminate the need for careful study of patients for at least four to six weeks after the onset of infection.

Our report is based on a study of 609 patients with scarlet fever. The study was designed to survey the age distribution, severity of the disease, the effect of treatment on the initial cultures for the isolation of Streptococcus pyogenes, the effectiveness of penicillin and sulfisoxazole in eradicating the streptococcus, the effect of these drugs on the fever, the frequency of complications, and the production of antibodies to two streptococcal antigens.

MATERIALS AND METHOD

The study includes 609 patients who were admitted to the Contagious Diseases Service of the Philadelphia General Hospital, Northern Division, during the period from November, 1951 to March, 1953. Only patients with an unequivocal diagnosis of scarlet fever were included in the study. The cases were classified into "mild," "moderate" and "severe" types according to severity as indicated by the day of disease, the height of the patient's fever and the intensity of the rash on the day of admission to the hospital. Patients with a temperature between 102° and 104°F. within five to seven days of onset of disease were classified as "moderate" cases; those with a temperature less than 102°F. as "mild"; and those with a temperature over 104°F. as "severe."

The three types were divided into three main treatment groups, namely, a penicillin group, a sulfisoxazole group and a control or symptomatically treated group. Of the 609 cases, 510 were of the mild, ninety-four of the moderate and five of the severe type. Patients with bacterial complications were assigned alternately to one of the specific treatment groups. Those without bacterial complications were assigned alternately to each of the three groups.

Routine blood and urine studies were performed in all patients. Nasopharyngeal cultures were taken from the nasopharynx with cotton-tipped flexible wire swabs; throat cultures were taken from the pharynx with cotton-tipped wooden applicators. All

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inocula were cultured on blood agar medium. Nasopharyngeal and throat cultures were taken immediately upon admission to the hospital. Throat cultures were repeated at five-day intervals for the duration of the hospital stay. Culture growths were examined grossly for hemolyzing colonies. Microscopic examinations of smears from the colonies were performed whenever Str. pyogenes could not be presumed to be present upon gross examination of the plates.

Electrocardiograms, x-rays and other laboratory studies were performed as indicated by the clinical course of the disease. Whole blood, for serologic studies, was drawn on admission and in the third and sixth week of disease.

Serologic Tests. Antihyaluronidase: The mucin-clot-prevention test was performed as described in detail elsewhere [*9*]. Successive two-fold dilutions of serum were made in volumes of 0.4 ml. To the serum was added 0.2 ml. of a solution of lyophilized concentrate of streptococcal culture supernate (group A hemolytic streptococcus, strain H-44) containing 3 units of hyaluronidase activity per 0.2 ml. The reagents were incubated at room temperature for fifteen minutes. Then 0.2 ml. of a 0.2 per cent solution of potassium hyaluronate (prepared by aqueous extraction of human umbilical cords) containing 10 per cent of horse serum was added to the tubes and the mixture was incubated at 37°C. for twenty minutes. The tubes were then quickly transferred to an ice-water bath. After five minutes of chilling, 0.2 ml. of 2N acetic acid was added to each tube. The racks were shaken vigorously and the tubes were examined for the presence of mucin clots. The appearance of a flocculent precipitate, indicating digestion of the hyaluronate, denoted an absence of antibody to hyaluronidase. The appearance of a full-sized clot (as judged by comparison with tubes containing hyaluronate and acetic acid but no hyaluronidase) indicated the presence of antibody which had neutralized the hyaluronidase. The inverse of the initial dilution of serum corresponding to the last tube which showed a full clot was considered the titer of the serum.

Antistreptolysin: The procedure used in performing the antistreptolysin O tests was essentially that suggested by Todd [*10*], with some modifications. Serum dilutions in serial two-fold steps were made in 0.4 ml. volumes. To this was added 0.2 ml. of streptococcal culture supernate (desiccated from supernates of cultures of group A hemolytic streptococcus, strain NY5) containing 1 mg. of sodium bisulfite. The concentration of the streptococcal preparation was adjusted so that the 0.2 ml. used had 3 units of hemolytic activity under the conditions of these tests. The mixture of serum and reduced hemolysin was incubated for fifteen minutes at room temperature, after which 0.2 ml. of an 8 per cent suspension of washed sheep erythrocytes was added. The racks were shaken and incubated at 37°C. for one hour. After allowing time for the red blood cells to settle, the degree of hemolysis was read. The inverse of the initial dilution of serum corresponding to the last tube which showed no hemolysis of red blood cells was considered the titer of the serum.

Treatment: Except for the type of antibiotic drugs used, all the patients received the same treatment.

TABLE 1
AGE DISTRIBUTION OF PATIENTS WITH SCARLET FEVER

Age Groups (Years)	Number of Patients	Distribution (%)
0– 4	224	36.8
5– 9	342	56.2
10–14	32	5.3
15–19	7	1.1
20–24	2	0.3
25–29	0	0
30–34	1	0.2
35–39	0	0
40–44	0	0
45–49	1	0.2
Total	609	100

Patients in the control or symptomatically treated group received no antibiotic drugs until a bacterial complication developed. The patients in the penicillin group were divided into two sub-groups. One sub-group of penicillin-treated patients was treated with 800,000 units of a commercial brand of penicillin (abbocillin®) intramuscularly, every other day for three doses. The other sub-group of patients was treated with a mixture of 600,000 units procaine penicillin G aqueous suspension and 200,000 units crystalline penicillin G, intramuscularly, every other day for three doses. The patients in the sulfisoxazole (gantrisin®) group received 60 mg. (1 gr.) per pound per day at six hour intervals for twenty doses, the initial dose being doubled.

RESULTS AND COMMENTS

Age Distribution of Patients. Of the 609 patients with scarlet fever admitted to the hospital during the period of this study, 36.8 per cent were between seven months and four years of age, and 56.2 per cent between five and nine years of age. These two groups comprised 93 per cent of the patients. The youngest patient in the study was seven months of age and the oldest was forty-nine years of age. (Table 1.)

Distribution of Patients According to the Day Treatment was Begun. In this series, 96.7 per cent of the patients were admitted and treated within the first five days of disease; 86.2 per cent were admitted within the first three days. The day of

admission indicated generally when the rash first became apparent. It is interesting to note that twenty-three (3.8 per cent) patients were admitted on the zero day of disease. (Table II.)

Distribution According to the Severity of the Disease. The patients were fairly evenly distributed among the groups, each group included approximately one-third of the total number of patients. There were 208 patients in the sulfisoxazole group, 227 patients in the penicillin group and 174 in the control group. The slightly uneven distribution of patients in the three groups was caused largely by the fact that no patients with complicated cases were assigned to the control group. (Table III.)

Of the patients with mild cases, 33.1 per cent were in the sulfisoxazole group, 35.7 per cent in the penicillin group and 31.6 per cent in the control group. The fairly even distribution of patients with mild scarlet fever among the three groups reflects the fact that bacterial complications in the mild group were few.

The distribution of patients with the moderate type of scarlet fever was 13.8 per cent in the control group, as compared with 39.4 per cent in the sulfisoxazole and 44.7 per cent in the penicillin group. The difference in the distribution of patients with the moderate type of disease between the control and the treated groups of patients is due to the exclusion of patients with complicated cases from the control group.

The number of cases of the severe type is too small to warrant an accurate statistical interpretation but is indicative of the comparative mildness of scarlet fever encountered.

Effect of Treatment before Admission on the Initial Culture. Of the 609 patients who were admitted, 255 received some form of antibiotic treatment and 319 received no specific antibiotic treatment before admission. Penicillin was used in 222 patients, 163 received it intramuscularly and fifty-nine orally. The number of doses administered before admission was not known in all cases but it can be presumed that each patient received at least one dose of the medication prescribed. In twenty patients a sulfonamide drug was used orally, in thirteen additional patients various other antibiotics or combinations of antibiotics were used. These included sulfonamides with penicillin, penicillin with oxytetracycline, penicillin with streptomycin, chlortetracycline, oxytetracycline and chloramphenicol. (Table IV.)

In the untreated patients, 64.9 per cent of 319 patients had a positive culture on admission.

TABLE II
DISTRIBUTION OF PATIENTS ACCORDING TO DAY OF DISEASE WHEN PATIENTS WERE ADMITTED TO HOSPITAL

Day of Disease	Sulfisoxazole	Penicillin (mixture)	Penicillin (brand)	Control	Total
0	9	4	6	4	23
1	66	29	34	42	171
2	72	32	52	49	205
3	36	12	26	52	126
4	10	11	8	17	46
5	8	2	6	2	18
6	5	1	0	1	7
7	1	1	1	2	5
Over 7	1	1	1	5	8
Total	208	93	134	174	609

TABLE III
DISTRIBUTION OF PATIENTS ACCORDING TO SEVERITY OF SCARLET FEVER AND TREATMENT

Severity	Sulfisoxazole	Penicillin			Control	Total
		Mixture	Brand	Total		
Mild....	169	80	101	181	160	510
Moderate	37	12	31	43	14	94
Severe...	2	1	2	3	0	5
Total....	208	93	134	227	174	609

TABLE IV
DISTRIBUTION OF PATIENTS ACCORDING TO CULTURES FOR STR. PYOGENES ON ADMISSION TO THE HOSPITAL

Initial Culture	No Treatment		Penicillin				Sulfonamides		Other Drugs	Total
			Intramuscular		Oral					
	No.	%	No.	%	No.	%	No.	%		
Positive..	207(1)*	64.9	36(2)	22.1	21(3)	35.6	13(4)	65	2	279
Negative.	112	35.1	127	77.9	38	64.4	7	35	11	295
Total..	319	100	163	100	59	100	20	100	13	574

* Standard error of the difference between
(1) and (4) is less than 1.
(1) and (2) plus (3) is greater than 9.
(2) and (3) is greater than 2.

This agrees substantially with the 69.5 per cent initial positive cultures in 139 scarlet fever patients reported by Jersild [*11*]. The patients who received a sulfonamide drug before admission showed 65 per cent positive cultures on admission to the hospital. This differs little from the 69.5 per cent initially positive cultures in the patients who received no antibiotic treatment before admission. On the other hand, only 22.1 per cent of the patients who received intramuscular penicillin and 35.6 per cent of the patients who received oral penicillin, had positive cultures when admitted to the hospital.

The difference between the rates of initially positive cultures of untreated patients (64.9 per cent) and the sulfonamide-treated patients (65 per cent) is small. There is a marked difference, however, in the rates of initially positive cultures between the patients who received some form of penicillin treatment (25.7 per cent) and the patients who were untreated (64.9 per cent). An analysis of the patients who received penicillin shows that intramuscular penicillin was 30 per cent more effective than oral penicillin in decreasing the frequency of positive cultures. This difference is highly significant statistically. (Table IV.)

In this series 588 patients had paired nasopharyngeal (NP) and throat (T) cultures for Str. pyogenes on admission. Of the 1,176 culture examinations performed, 397 (33.8 per cent) were positive and 779 (66.2 per cent) were negative. Our interests were directed towards the effectiveness of the two methods of examination for the isolation of the organism, and the influence of the presence of tonsils and adenoids on the results. Eighteen of the 588 patients who had paired NP and T culture examinations had had an adenoidotonsillectomy, 570 had intact tonsils and adenoids. In the adenoidotonsillectomized patients, ten (55.5 per cent) of eighteen NP cultures were positive, compared with nine (50 per cent) of eighteen T cultures. The difference in the rates of the positive cultures is small but is not statistically significant. (Table v.)

In 570 patients with intact tonsils and adenoids, 137 (24 per cent) of 570 NP cultures were positive, as compared with 241 (42.3 per cent) of 570 T cultures. The difference between the rates of positive throat cultures and nasopharyngeal cultures in patients with intact tonsils and adenoids is marked and is highly significant statistically. Evidently, throat culture examination was superior to NP examination for the isolation of Str. pyogenes in scarlet fever patients with intact tonsils and adenoids. A comparison of the rates of positive T cultures in patients with and without tonsils and adenoids showed a negligible difference which was not statistically significant. On the other hand,

TABLE V
RESULTS OF NASOPHARYNGEAL (NP) AND THROAT (T) CULTURES FOR STR. PYOGENES ON ADMISSION IN ADENOIDOTONSILLECTOMIZED AND NON-ADENOIDOTONSILLECTOMIZED PATIENTS

Cultures	Adenoido-tonsillectomized		Non-Adenoido-tonsillectomized		Total
	NP	T	NP	T	
Positive.....	10 (1)*	9 (2)	137 (3)	241 (4)	397
Negative....	8	9	433	329	779
Total.....	18	18	570	570	1176

* Standard error of the differences between
(3) and (4) is greater than 6.
(2) and (4) is less than 1.
(1) and (3) is greater than 3.

NP cultures yielded a higher rate of positives in the adenoidotonsillectomized patients than in the non-adenoidotonsillectomized patients, a difference which is marked and highly significant statistically. (Table v.)

NP cultures were not superior to T cultures in adenoidotonsillectomized patients, while T cultures were superior to NP cultures in patients with intact tonsils and adenoids. It is concluded that NP cultures offer no advantage over T culture examinations for the isolation of Str. pyogenes in scarlet fever patients either with or without tonsils and adenoids. This conclusion is in accord with the concept that scarlet fever is initially and primarily an infection of the throat.

It appears to be self-evident that eradication of Str. pyogenes from the upper respiratory tract should prevent transmission of the infection to other persons. The effect of treatment on the throat and NP cultures was studied to determine the value of treatment as a prophylactic measure, to determine the correlation of the cultures with the frequency of bacterial complications, the production of specific immune antibodies and the development of nephritis and rheumatic fever.

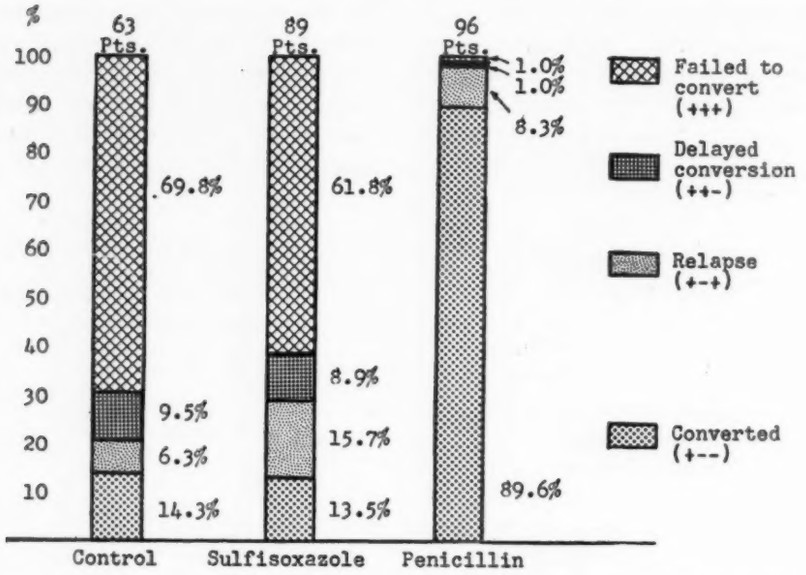

FIG. 1. Percentage distribution of patients in the three groups according to the conversion from positive to negative cultures. Cultures were taken at five day intervals.

The effectiveness of penicillin and sulfisoxazole in eradicating streptococci from the upper respiratory passage was studied in 248 patients who had a positive culture on admission. Forty-four (69.8 per cent) of sixty-three control patients had positive cultures on the fifth and tenth days after admission, which compares with fifty-five (61.8 per cent) positive cultures of eighty-nine patients who were treated with sulfisoxazole, and only one (1 per cent) positive culture of ninety-six patients who were treated with penicillin. The difference in the rates between the control and the sulfisoxazole-treated patients was small but not statistically significant. However, the difference between the rates of positive cultures in patients after treatment with penicillin and the control or sulfisoxazole-treated patients, was large and is statistically significant. (Table VI.)

TABLE VI
DISTRIBUTION OF PATIENTS IN THREE GROUPS ACCORDING TO CULTURE PATTERN IN FIRST TEN DAYS OF TREATMENT

Culture Pattern	Control		Sulfisoxazole		Penicillin		Total
	No.	%	No.	%	No.	%	
+−−	9	14.3 (1)*	12	13.5 (2)	86	89.6 (3)	107
+−+	4	6.3	14	15.7	8	8.3	26
++−	6	9.5	8	9.0	1	1.0	15
+++	44	69.8	55	61.8	1	1.0	100
Total...	63	100.0	89	100.0	96	100.0	248

* Standard error of the difference between
(1) and (2) is less than 1.
(1) and (3) is greater than 10.
(2) and (3) is greater than 10.

Of the patients in whom the culture failed to convert from positive on admission to negative on the fifth and tenth days after admission, in some the culture became negative on the fifth day only and in some on the tenth day only.

The rates of conversion from positive culture on admission to two consecutive negative cultures were nine (14.3 per cent) of sixty-three control patients, twelve (13.5 per cent) of eighty-nine sulfisoxazole-treated patients and eighty-six (89.6 per cent) of ninety-six penicillin-treated patients. The percentage of patients in the control and sulfisoxazole-treated groups in whom the culture converted is small but it is comparable in the two groups. The difference between these rates is only 0.8 per cent but is not statistically significant. In the penicillin-treated patients, on the other hand, there was a higher rate of conversion to two negative cultures, the difference in the rates between the penicillin-treated and the control patients being 74.3 per cent and between the penicillin- and the sulfisoxazole-treated patients, 76.1 per cent. These differences are marked and are highly significant statistically. (Fig. 1.)

In twenty-six of 248 patients with positive cultures on admission, the cultures became negative on the fifth day and reverted to positive on the tenth day. In the control group four (6.3 per cent) of sixty-three patients showed a similar relapse, while fourteen (15.7 per cent) of eighty-nine sulfisoxazole-treated patients had a relapse. The reversion of the cultures from negative on the fifth day to positive on the tenth day indicates either reinfection or relapse. The higher rate of relapse in the treated groups of patients as compared with the control group might be the result of inadequate effect of the antibiotics because of the bacterial complications in these groups of patients. The difference in the rates between the treated groups is not statistically significant, whereas the difference between the rates of the treated and the control patients is on the borderline of significance.

In fifteen of the 248 patients, there was a conversion to negative cultures on the tenth day only. In the control group this delayed conversion occurred in six (9.5 per cent) of sixty-three patients as it did in eight (9 per cent) of eighty-nine patients in the sulfisoxazole group and in only one (1 per cent) of ninety-six patients in the penicillin-treated group. The lower rate of delayed conversions in the penicillin-treated patients is statistically significant.

There was no difference in the duration of fever in the patients with mild cases of complicated scarlet fever who were treated with either penicillin or sulfisoxazole. In the moderate type of complicated scarlet fever, the duration of fever was shorter in the penicillin-treated than in the sulfisoxazole-treated patients, the average duration of fever for each patient being 1.88 days in the former group and 3.40 days in the latter group. This difference represents almost a 50 per cent shorter febrile period in the penicillin-treated patients, a difference which is highly significant. Although there are only five patients with the severe type of complicated scarlet fever in the study, an effect on the duration of fever comparable to that seen in the moderate type was noted. Further evidence demonstrating the beneficial effect of penicillin on the duration of fever is the shorter febrile period in the penicillin-treated patients with mild and moderate types of scarlet fever (despite complications) than in the control group, which averaged 1.53 days per patient for the mild type, and 2.37 days for the moderate type. Sulfisoxazole-treated patients with complications showed a shorter course of fever than did the uncomplicated controls in the mild type but had a longer course of fever in the moderate type. (Table VII.)

There was essentially one type of complication that developed in the patients, namely, infectious complications predominantly of streptococcal etiology. Non-infectious complications, presumably triggered by or resulting from streptococcal infection, are rheumatic fever and glomerulonephritis. Of the infectious complications, those of bacterial origin included otitis media, pharyngitis, tonsillitis, cervical adenitis, sinusitis, rhinitis, peritonsillitis, paronychia, dermatitis, bronchopneumonia, bronchitis and conjunctivitis. The non-bacterial infections consisted of coincidental virus infections like measles, mumps, herpangina, varicella and toxic, allergic and non-infectious dermatologic conditions. The number of bacterial complica-

TABLE VII

DURATION OF TEMPERATURE OVER 100°F. IN PATIENTS WITH COMPLICATED CASES OF SCARLET FEVER ACCORDING TO TYPE OF DISEASE AND TREATMENT

Severity of Disease	Observed Days of Fever	Number of Patients	Days Fever per Patient	Expected Days of Fever
Sulfisoxazole Group				
Mild	102	74	1.38	129.5
Moderate	126	37	3.4	64.8
Severe	3	2	1.5	3.5
Total	231	113	....	197.8
Penicillin Group				
Mild	124	90	1.38	157.5
Moderate	79	42	1.88	73.5
Severe	2	3	0.67	5.3
Total	205	135	....	236.3
Total Sulfisoxazole and Penicillin Groups				
Mild	226	164	1.38	287
Moderate	205	79	2.37	138.3
Severe	5	5	1.0	8.8
Total	436	248	1.75	434.1

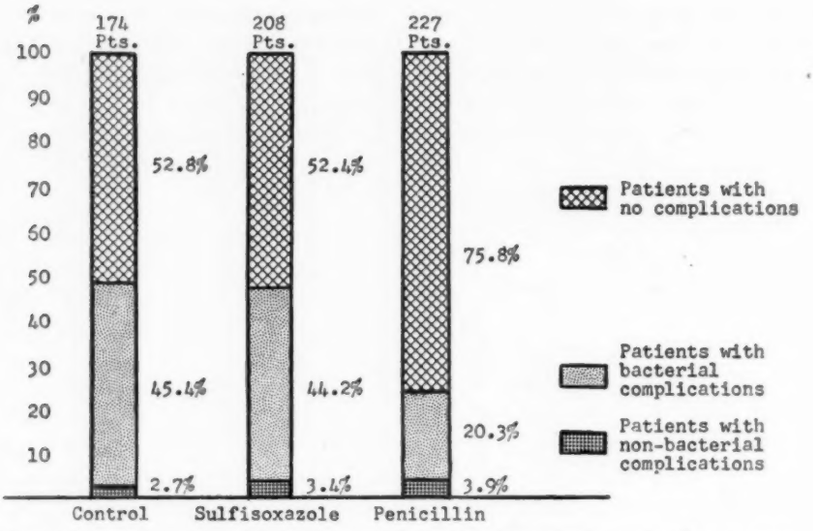

FIG. 2. Percentage distribution of patients in the three groups according to complications which developed after admission to the hospital.

tions far outnumbered the non-bacterial infectious ones; there were 217 of the former and only twenty-seven of the latter types.

There were no cases of rheumatic fever or glomerulonephritis in this study. In one fourteen year old patient with mild scarlet fever in the control group arthritis developed late in the course of his scarlet fever. Thorough examination and prolonged observation failed to show evidence that the arthritis was anything other than a toxic manifestation of scarlet fever. In another patient, a six year old child with scarlet fever, generalized urticaria developed on the fourth day of disease after two days of treatment with sulfisoxazole. Prompt recovery followed withdrawal of the drug. This was the only patient of 208 patients, a rate of 0.5 per cent, treated with sulfisoxazole in whom an allergic reaction developed. Sulfisoxazole had to be discontinued in another patient who was unable to retain the drug. In one of the ninety-three patients treated with penicillin (1 per cent) a local reaction developed to the intramuscular inoculation.

Bacterial complications developed in 217 of the 609 patients in the study. Broken down into groups bacterial complications developed in seventy-nine (45 per cent) of 174 control patients compared with ninety-two (44.2 per cent) of 208 sulfisoxazole-treated patients, and only forty-six (20.3 per cent) of 227 penicillin-treated patients. (Fig. 2, Table VIII.) The incidence of complications in the penicillin-mixture and penicillin-brand groups was 19.4 per cent and 20.9 per cent, respectively, a difference which is slight and not significant statistically. Apparently, there is no difference between the mixture and brand forms of penicillin used in these patients in respect to prevention of bacterial complications. The difference in the rates of complications between the penicillin-treated patients and the controls is marked and significant. In the penicillin-treated patients only 44.7 per cent of the expected number of complications developed whereas in the sulfisoxazole-treated patients 91.4 per cent of the expected number developed. It is apparent that sulfisoxazole had no effect in preventing bacterial complications and that penicillin was markedly effective in this respect. The ability of penicillin to decrease the incidence of bacterial

TABLE VIII
DISTRIBUTION OF COMPLICATIONS WHICH DEVELOPED AFTER ADMISSION TO HOSPITAL IN MILD AND MODERATE CASES OF SCARLET FEVER IN THE THREE GROUPS

Group	Number of Patients	No Complications	Bacterial Complications	Non-Bacterial Complications
Sulfisoxazole	208	109	92	7
Penicillin	227	172	46	9
Control	174	92	79	3
Total	609	373	217	19

complications is compatible with our findings which show that patients treated with penicillin before admission to the hospital had a lower rate of positive cultures for Str. pyogenes on admission. This fact implies a direct relationship between the presence of the streptococcus in the upper respiratory passage and the development of bacterial complications in scarlet fever.

Changes in Antistreptolysin and Streptococcal Antihyaluronidase Titers. Serums were obtained from 470 patients included in this study, at the time of admission to the hospital and approximately three weeks later. The levels of antibody to streptococcal hyaluronidase and hemolysin were determined for each pair of serums. The change in titer of antibody from onset to three weeks later for each pair was tabulated. To evaluate the serologic changes, which had been computed in units of half a two-fold step of serum dilution, certain groups were combined. Thus those pairs of serums which showed a fall in titer, no change at all, and only half a two-fold step rise (which was considered to be within the margin of error of the technic) were grouped together. Those pairs which showed a rise in titer of two two-fold steps or more were considered to indicate a significant serologic response to the infection and were grouped together. Between these groups were the pairs of serums which showed a one or one-and-a half in titer two-fold step rise, indicating a slight response. When all the changes were tabulated within these groupings, it was found that of the 140 control patients tested for streptococcal antihemolysin 35.6 per cent showed a fall or no change in titer, compared with 40.7 per cent of the 167 patients treated with sulfisoxazole and 62.1 per cent of the 163 patients treated with penicillin. The comparable percentages in the streptococcal antihyaluronidase test were 55.1 for the control group, 62.8 for the sulfisoxazole and 77.9 for the penicillin group. Within each treatment group the pairs of serums which showed a significant rise in antistreptolysin titer were 47.2 per cent in the control group, 42.6 per cent in the sulfisoxazole group and 20.5 per cent in the penicillin group. In the antihyaluronidase test the analogous percentages were 29.2 for the controls, 30.0 for the sulfisoxazole group and 14.1 for the penicillin group. These findings are shown in Figure 3.

Thus it can be seen that the administration of penicillin to the patients with scarlet fever for five days after admission to the hospital had a decided effect on the antibody response to two streptococcal antigens in the first three weeks of the disease. This is consistent with earlier reports by others [*12*]. The serologic changes in the group of sulfisoxazole-treated patients resemble more closely those of the control group but do show a slight reduction in the antibody response to the two antigens. The difference in the effects of penicillin and sulfisoxazole on the antibody response is consistent with the difference in mode of action of these drugs on streptococci. Since sulfisoxazole is bacteriostatic, it is possible that organisms which cannot multiply continue to metabolise sufficiently to produce amounts of the streptococcal antigens adequate to cause antibody production. The serologic effect of the administration of these drugs can be seen in the results of both the antistreptolysin and antihyaluronidase tests.

Serums were obtained six weeks after the onset of symptoms from 181 of the patients studied. In the antistreptolysin test in approximately 83 per cent of the patients in all groups there was a fall or no change in titer from the three-week serum sample. Of the control group, in 6.4 per cent (of sixty-two patients) there was a significant rise above the three-week level. The analogous percentages for the sulfisoxazole group was 10.3 (of sixty-nine patients) and for the penicillin group 6.0 (of fifty patients). In the antihyaluronidase test, in 85.5 per cent of the control group there was a fall or no change in titer compared with 88.4 per cent in the sulfisoxazole group and 92.2 per cent in the penicillin group. Within the control group, in 1.6 per cent of the patients there was a significant rise from the three-week level to the six-week level, 4.4 per cent in the sulfisoxazole group and 3.9 per cent in the penicillin group. These findings are shown in Figure 3.

It is of interest to note that within the control groups the serologic changes observed indicate different responses to the two streptococcal antigens. In the antistreptolysin test 47.2 per cent of the pairs of serums showed a significant rise in titer, in comparison with 29.2 per cent in the antihyaluronidase test. Also, in 35.6 per cent of the control patients there was a fall or no rise in titer in the antistreptolysin test compared with 55.1 per cent in the antihyaluronidase test. These findings are consistent with an earlier observation reported in which it was found that serologic response to streptococcal hyaluronidase

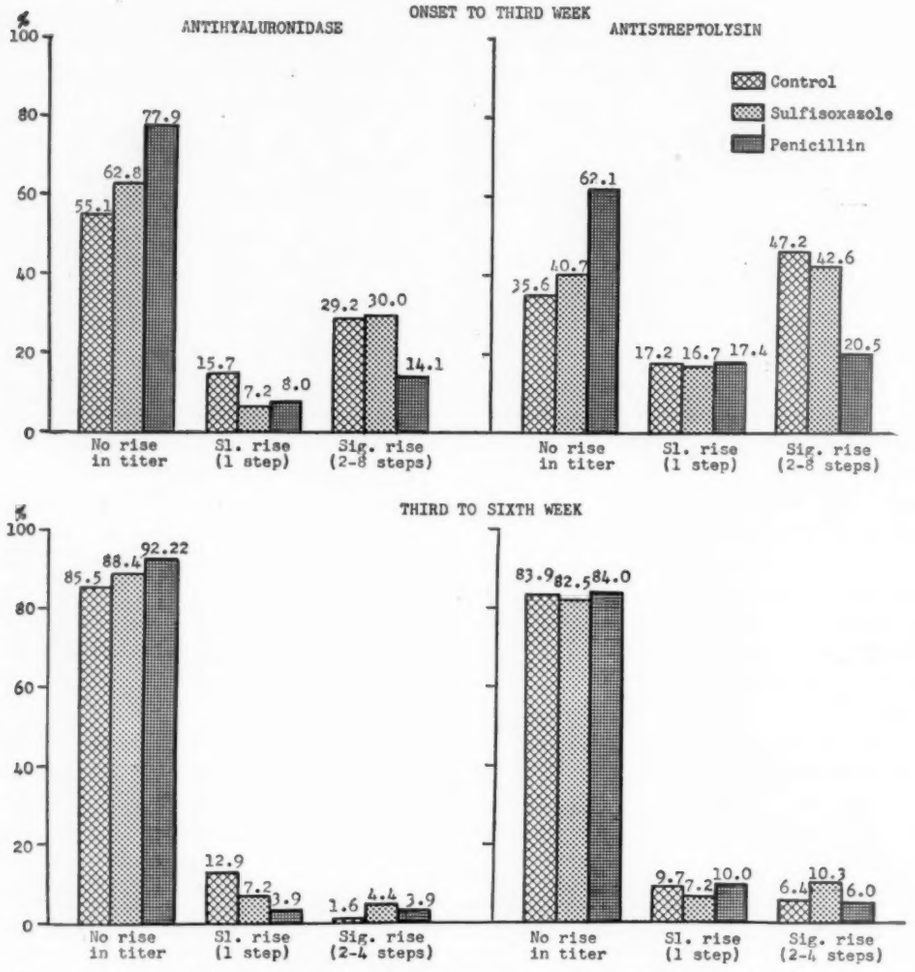

FIG. 3. Percentage distribution of serologic changes in scarlet fever in treated and untreated patients. The serum dilutions for the antihyaluronidase and antistreptolysin tests were performed in serial two-fold steps and differences in titer are shown in terms of such steps.

in scarlet fever was less marked than that to streptococcal hemolysin [*13*].

COMMENTS

The percentage of untreated patients with initially positive cultures for Str. pyogenes in this study was 64.9 per cent compared with 69.5 per cent reported by Jersild [*11*] and 69 per cent by Garcia [*3*]. These rates are significantly lower than the 85 per cent positive throat cultures of one hundred scarlet fever patients reported by one of us in 1949 [*14*]. It is difficult to account for the differences in the rates. Variations in the technic of swabbing, inoculation of the medium and delay in getting the cultures to the incubator are factors which may affect the percentage of positive cultures. In any case, it is expected that the chances of obtaining a positive culture for Str. pyogenes from an untreated scarlet fever patient are relatively good, provided reasonable care is taken to obtain an adequate specimen from the throat. According to the results of this study, the chances of obtaining a positive culture for Str. pyogenes from the throat of a scarlet fever patient are not diminished at all by sulfisoxazole therapy.

The lower incidence of initially positive cultures in patients treated with intramuscular injection of penicillin than in patients treated with oral penicillin before admission is due to the differences in the utilization rates by the two routes of administration; the intramuscular route resulting in a more effective blood level in a dose-for-dose comparison with the oral route. Approximately one-half of our patients were treated with either an antibiotic or sulfon-

amide drug before admission to the hospital, the majority of the patients having received penicillin intramuscularly.

The effectiveness of penicillin in eradicating Str. pyogenes from the throat is apparent from our results. These results are consistent with the findings of Rhoads, Sibley and Billings [*16*] who reported positive cultures in 28.3 per cent of sixty-eight untreated control patients but in only one of fifty-six penicillin-treated pretonsillectomy patients. These authors showed also, by cultures of excised tonsils, that hemolytic streptococci could still be cultured from 57.4 per cent of untreated patients, whereas they were eradicated in nearly all patients after four to ten days of penicillin therapy.

No cases of rheumatic fever or glomerulonephritis were diagnosed in our study during the patients' hospital stay. It is admitted that the period of observation was not long enough to rule out definitely these complications. Since we were unable to examine these patients personally to evaluate their cardiac status after discharge from the hospital, we examined the records of the rheumatic fever cases reported to the Section on Communicable Disease Control of the Philadelphia Health Department, to which agency this disease is reportable by regulation of the Board of Health. It is believed that nearly all cases of rheumatic fever in the school population (five to fourteen years of age) are known to the Health Department because of the intense and concentrated efforts of the Medical Division of the school system to detect rheumatic fever in its pupil population. Between 60 per cent and 70 per cent of all cases of rheumatic fever reported to the Health Department are between five and fourteen years of age. None of the patients in our study were reported with rheumatic fever to the Health Department [*17*].

Our criteria for the diagnosis of rheumatic fever and glomerulonephritis were not as rigid as those of Weinstein, Bachrach and Boyer [*8*], which accounts, in part, for the comparatively lower incidence of these complications in our patients. According to the expected rate (3 per cent) of complications for streptococcal infections, we should have had about twelve patients with cardiac and renal complications in the 382 control and sulfisoxazole-treated patients.

The suppressive action of penicillin on the production of antihyaluronidase and antistreptolysin antibodies, and the eradication of streptococci from the throats of our patients are evidence of the bactericidal activity of this antibiotic. There is no apparent direct relationship between antistreptolysin and acute rheumatic fever. Catanzaro et al. [*15*] have demonstrated that acute rheumatic fever can be prevented by penicillin, even though treatment is delayed as long as nine days after the onset of infection, without interfering significantly with the production of antistreptolysin antibodies. Accordingly, it is presumed that streptococcus streptolysin is probably not the cause of rheumatic fever but probably some other antigen which is susceptible to penicillin.

SUMMARY

Scarlet fever is a relatively mild disease. Most scarlet fever patients have the "mild" type of infection, many have the "moderate" type, and few have the "severe" type of the disease.

Penicillin, given orally or intramuscularly, even in one dose, reduces the number of positive cultures for streptococci from the nose and throat; intramuscular penicillin is superior to oral penicillin in this respect. When used in one dose, the sulfonamide drugs do not eradicate streptococci from the nose and throat.

Throat cultures yield a higher rate of positive results for Str. pyogenes than do nasopharyngeal cultures in patients with intact tonsils and adenoids. Throat cultures are at least as effective as nasopharyngeal cultures for the isolation of the organism in patients without tonsils and adenoids.

Penicillin, given intramuscularly, was markedly effective in eradicating streptococci from the nose and throat of scarlet fever patients. Sulfisoxazole is incapable of producing this result. Penicillin, more than sulfisoxazole, shortened the febrile period of patients with the moderate and severe types of scarlet fever. Sulfisoxazole failed to prevent bacterial complications in scarlet fever, whereas penicillin had a marked effect on lowering the incidence of bacterial complications.

Untoward reactions to penicillin and sulfisoxazole were rare in this series.

In comparisons of the serologic response to streptococcal hemolysin and hyaluronidase among patients of the three treatment groups it was found that during the first three weeks of the disease the group treated with penicillin showed considerably smaller antibody response than did the control group. In a large percentage

of penicillin-treated patients there was no change in titer, and in a small percentage there was a significant rise, as compared with the control group. The changes in the group treated with sulfisoxazole resembled those of the control group but there was a small reduction in antibody response.

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Seminar on Bone Disease

A Survey of Bone Disease*

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A FITTING introduction to any consideration of bone disease is found in a paragraph with which Eduard Rindfleisch began a discussion of disturbances of the skeletal system in his "Manual of Pathological Histology," which appeared almost a hundred years ago [*1*]. "Whoever is familiar with the interesting series of histological alterations which accompany the normal development of the skeletal system, with all that is known concerning growth of bone from periosteum and the transformation of cartilage into bone, already has knowledge of the fundamental pathological histology of the osseous system, and can find his way with ease among the minor qualitative deviations from the normal type, which nevertheless exist." We shall briefly review normal growth sequences in cartilage and bone; for if such are understood, a satisfactory classification of bone disease can then be formulated.

Virtually the entire bony skeleton is derived from cartilage. This transformation, which is termed endochondral bone formation, goes on during intrauterine development as well as for many years after birth. We shall take as an example the development of a single bone, the humerus, drawing freely on Streeter's now classic description [*2*].

In the early embryo (approximately the 25 somite stage), mesoblastic cells begin to condense beneath the epithelium of the body wall in four distinct areas. These sites represent the primitive limb buds. As these mesoblastic cells proliferate, the overlying epithelial elements also increase in number. Next, the cells in the center of each bud further differentiate and so become the skeletal primordium which by this time is already surrounded by clearly demarcated muscle masses. The cells of the skeletal primordium soon become recognizable as cartilage. They are invested by less differentiated elements which make up the perichondrial layer. With the continual proliferation of cartilage cells, a miniature of the future humerus is formed. (Fig. 1.) At this stage one can recognize distinct areas in which the cartilage cells have reached different degrees of development. Dr. Streeter divided the cells arbitrarily into five groups, depending primarily on their size and location. As this cartilagenous replica of the humerus increases in mass, its central or mid-portion comes to be invested by a collar or bone, which is formed by the perichondrial cells in this region. Soon this bony shell is eroded from without by blood vessels and connective tissue cells; the former then begin the destruction of the largest or hypertrophic cartilage cells, thus initiating the formation of a marrow cavity.

These sequences give rise to a tube of bone (the diaphysis) which is capped on each end by cartilages (the epiphyses). The junction between the diaphysis and epiphysis is called the metaphysis; it represents the area of most active bone growth. If one examines this region of the cartilage-shaft junction in more detail, a very orderly picture is found. (Fig. 2.) The cartilage cells grow larger and, as one goes toward the shaft, come to be arranged in parallel rows. In the organic matrix material between the cell rows, inorganic salts are deposited. Into this sort of honeycomb, capillaries which are accompanied by cells grow and replace the cartilage cells. On the framework of calcified cartilagenous matrix, bone matrix, which is called osteoid, is formed by the osteoblasts which follow the blood vessels. Since inorganic materials are rapidly deposited in this osteoid, bone results. Were there not some means of destroying a large part of the calcified cartilage matrix covered by bone, the entire skeleton would be inordinately dense. Fortunately, destruction which is mediated by osteoblasts and

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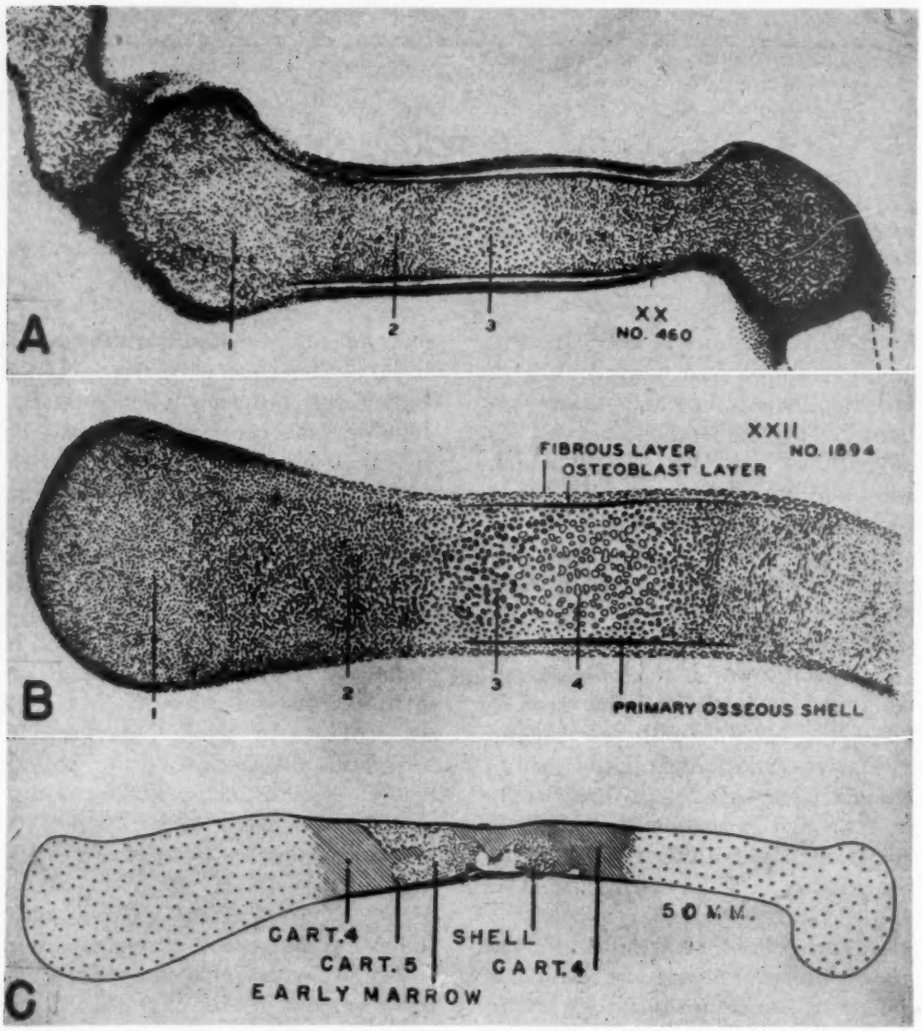

FIG. 1. Three stages in the development of the humerus in the human (from Streeter [2]). A, section through the entire humerus from a 21 mm. embryo to show resemblance of shape to final form. Note zones of cartilage in three stages of development. B, similar preparation from a 24.6 mm. embryo to show further growth of cartilage and appearance of bony shell in mid-portion of shaft. C, humerus reconstructed from a 50 mm. fetus to show appearance of marrow cavity as a result of the destruction of the most mature cartilage cells.

osteoclasts occurs in the metaphysis so that only a small part of the original structure is retained.

From this brief summary of normal osteogenesis several important processes are seen to be in operation: (A) growth of the cartilage, (B) deposition of inorganic materials (hydroxyapatite) in the matrix of a certain area of this cartilage, (C) the formation of bone matrix on such a framework, (D) its immediate calcification, and (E) destruction of a large part of this calcified cartilage matrix encased in bone.

Down in the shaft, bone is continually being remodeled in its interior (endosteum) as a result of the activities of osteoblasts and osteoclasts. So, too, new matrix is being deposited on the surface by periosteal cells. We can not go into the internal transformation of the osteones at this time. Space does not permit a discussion of the chemical morphology of the cartilage cell, the osteoblasts and their respective matrices. Nor shall we review what little is known of the formation of these latter organic substances. The calcification mechanism and the composition of bone salt are subjects of utmost importance which have already been discussed in this symposium.

However, even with our meager background we are in a position to discuss some examples of the commoner bone diseases. Moreover, we

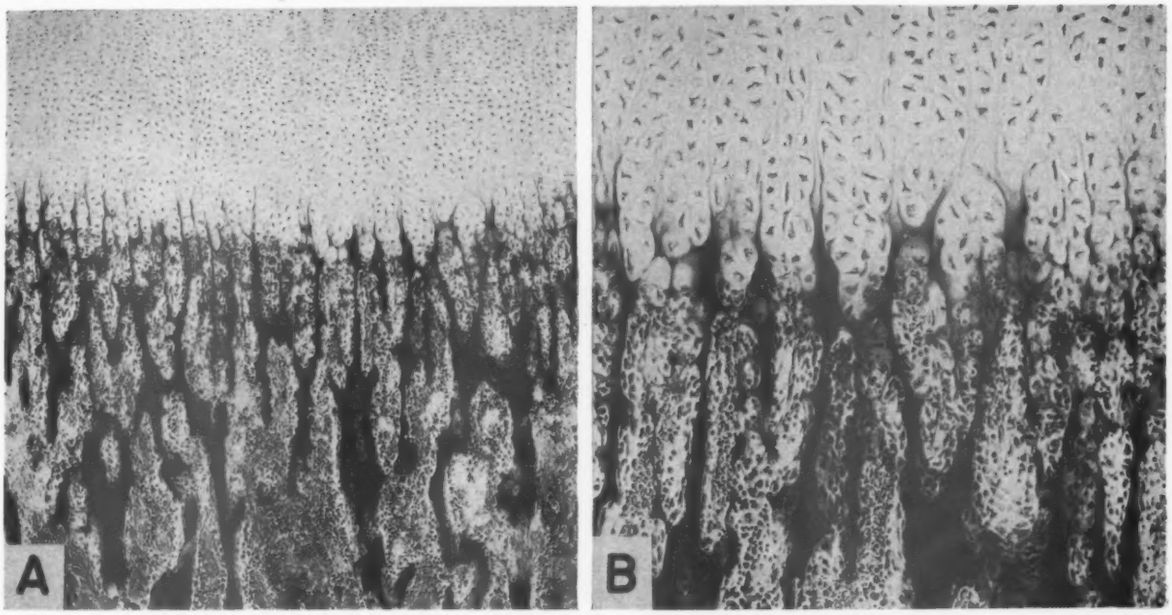

FIG. 2. A, low (× 50) and B, high (× 100) power photomicrographs of costochondral junction from a month old normal infant (HLH 520). Note increasing size and orderly arrangement of cartilage cells, presence of dark-staining material (hydroxyapatite) in the intercellular matrix, invasion of cell columns by capillaries, and deposition of bone on calcified cartilage matrix framework.

can place them into a satisfactory system of classification, divided among the following categories: (I) disturbance in the growth of cartilage; (II) disturbance in the osteogenic-osteolytic balance; and (III) disturbance in the deposition of hydroxyapatite in cartilage matrix and/or osteoid.

As is true of any classification, many diseases do not fit rigidly into one of these main groups. Yet, excluding primary tumors and inflammatory conditions, particularly congenital syphilis, one can formulate a satisfactory cubbyholing of bone disease, whether it be on a genetic, physical, metabolic, nutritional, endocrine or some other basis. Those diseases which fall into group I are of primary interest to the pediatrician. Those in group II are more likely to come to the attention of the internist. Both specialists are interested in the fundamental skeletal change which exemplifies group III.

We shall consider only those diseases which have been described in man. Although any number of interesting lesions have been produced in experimental animals by dietary deficiencies, hormone administration, feeding or the injection of toxic materials, and other means, descriptions of these would take us too far afield. Suitable references are given, whether or not we discuss each human disease in question. It is hoped that the illustrations will serve to indicate the few and rather stereotyped reactions which may be found under the microscope.

DISTURBANCES IN THE GROWTH OF CARTILAGE

Table I summarizes that group of bone diseases in which defective growth of cartilage is the outstanding fault. As is usual in classifying disease, we are here confronted with too much or too little of the normal. This is the group of the giants and dwarfs; the latter are more common. Hereditary, nutritional and endocrine factors all play an important role. Since little is known of the metabolic activities which characterize the growth of normal cartilage, we have virtually no understanding of the deranged patterns in those diseases which will be discussed subsequently.

The classic example of excessive growth activity of cartilage is furnished by the hyperpituitary state, provided it commences in childhood or at least before growth of the epiphyseal cartilage has stopped [*3*]. The stimulation of cartilage by growth hormone leads to excessive increments in length of the long bones, such as gigantism. The metabolic events whereby growth hormone achieves this end are completely unknown. The other situations which are associated with excess growth of the epiphyseal cartilages are also

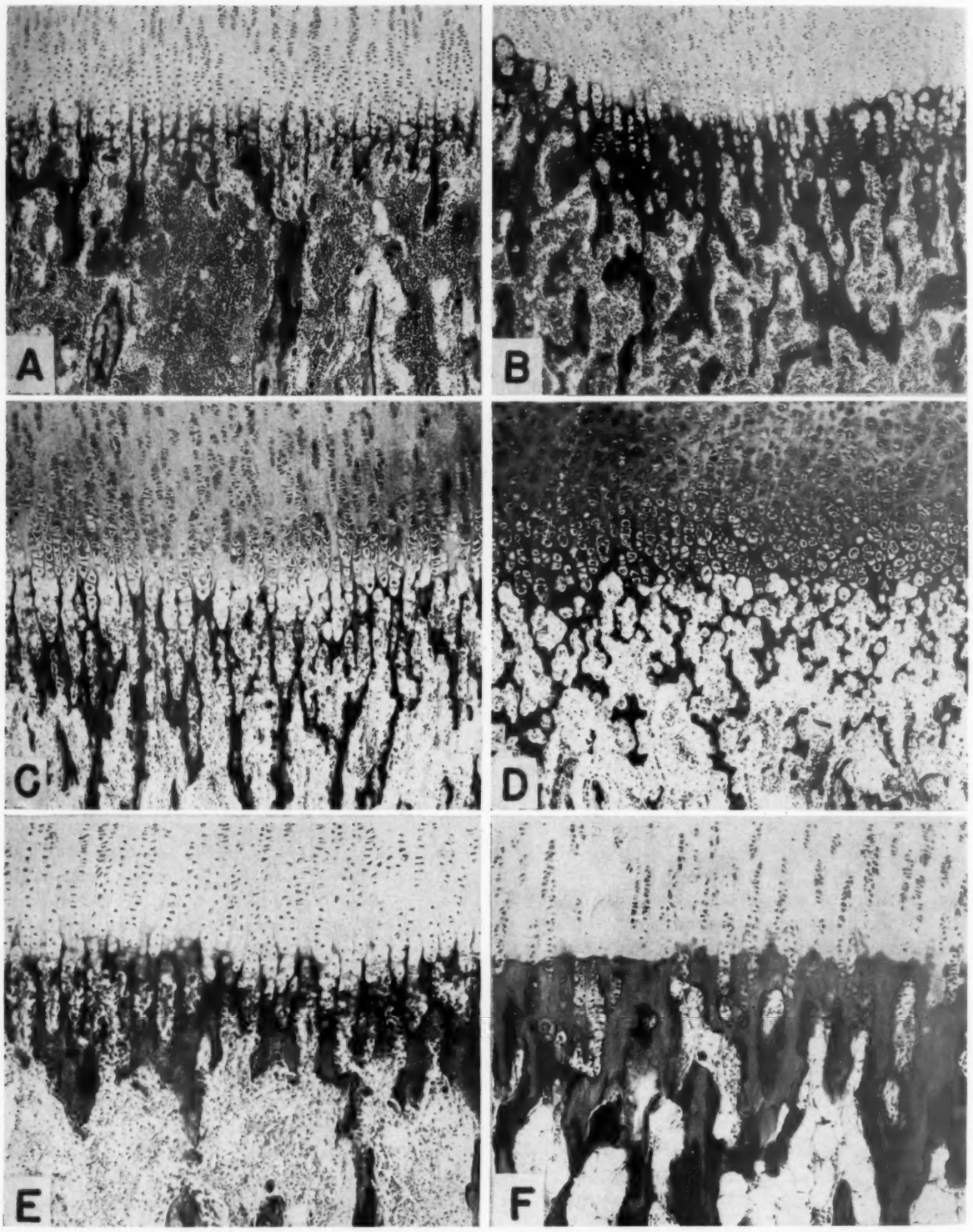

FIG. 3. A, costochondral junction from a poorly nourished month old infant dying of purulent meningitis (HLH 464, × 50). Compare with Figure 2A. Note decrease in width of hypertrophic cell layer and decreased amount of calcified cartilage matrix encased bone. Fewer osteoblasts are seen. B, costochondral junction from a month old infant dying of sinus thrombosis (HLH 415, × 50). Compare with Figure 2A. Note heavy zone of calcified matrix or "lattice" on which little bone is being deposited. This results because the cartilage grows and inorganic materials deposit in it, but none is removed as a result of decreased cellular activity below. C, lower end of femur from a normal newborn infant (HLH

of endocrine origin and are familiar enough [*4,5,6,7*]. It need only be pointed out that hypergonadal or hyperadrenal effects first lead to excessive growth; later on, as the cartilages mature and the epiphyses fuse, they do so prematurely; thus the end result is a stunted individual.

TABLE I
DISTURBANCES IN GROWTH OF CARTILAGE (CHONDRODYSPLASIA)

A. Increased Activity
Endocrine:
Hyperpituitarism [*3*]
Hyperthyroidism [*4*]
Hyperandrogenism
Adrenal [*5*]
Testis [*6*]
Hyperestrogenism [*7*]
B. Decreased Activity
Genetic:
Dyschondroplasia group
Chondrodystrophy fetalis [*8*]
Hunter-Hurler syndrome [*9*]
Osteochondrodystrophia deformans [*10*]
Chondroectodermal dysplasia [*11*]
Chondrodystrophia calcificans congenita [*12*]
Progeria [*13*]
Constitutional dwarfism [*14*]
Pseudohypoparathyroidism syndrome [*15*]
Gonadal dysgenesis syndrome [*16*]
Physical:
Radiation [*17*]
Nutritional:
Lack of essential nutrients, dietary or conditioned or caloric restriction [*18*]
Transverse line formation [*19*]
Immobilization [*20*]
Endocrine:
Hypopituitarism [*21*]
Hypothyroidism [*22*]
Cushing's syndrome [*23*]

As shown in Table I, a number of factors are associated with decreased activity of the growth of cartilage, the basis of which is doubtless some metabolic defect, although here again the precise derangement has in no case been elucidated. From this group one can take as the classic example a hereditary disturbance, achondroplasia (chondrodystrophy fetalis) [*8*]. In this condition, microscopically, the cartilage cells appear to be growing much more slowly than normal. (Fig. 3.) That is, each row of cells is short; so, too, the number of hypertrophic cells is reduced. Actually, the epiphyseal or costal cartilage resembles that from an older individual. In contrast, osteoblastic activity is perfectly normal, so much so that periosteal bone may extend up as a sort of collar about the epiphyseal cartilage. So, too, the cortex of the diaphysis may be thickened. The classic chondrodystrophic dwarf has few if any other congenital defects. However, other types of the chondrodysplastic group do exhibit abnormalities in additional areas. The Hunter-Hurler syndrome [*9*] is characterized by widespread infiltration of the tissues with ăn abnormal material, together with mental retardation, cardiac malformation, eye changes, alterations of the skin and the like. The syndrome, chondroectodermal dysplasia [*11*], as the name implies, has, in addition to chondrodysplasia, defects elsewhere, such as the nails and teeth.

Stunting of growth, which is probably not associated with a true genetic disturbance in the development of cartilage, is encountered in two other well defined syndromes: pseudo-hypoparathyroidism [*15*] and ovarian dysgenesis (Turner's syndrome) [*16*]. In neither is there any evidence that endocrine disturbance plays a role.

The effects of x-ray therapy on cartilage growth have been observed in children subjected to such treatment [*17*]. The metabolic defect here is unknown.

Cartilage is extremely susceptible to generalized disturbances in nutrition. One may therefore expect to encounter profound effects when any one of the essential nutrients, whether it be an element, amino acid, vitamin or fatty acid, is lacking from the diet [*18*]. Caloric restriction has an idential effect. Under such circumstances one is also likely to find that osteoblastic activity is similarly deranged, although this is not necessarily always the case. If cartilage growth stops,

1378, × 50). D, lower end of femur of newborn chondrodystrophic infant (HLH 1264, × 50). Compare with C. Note disorganization of cartilage with absence of row formation. Less intercellular matrix is present; hence a diminished amount of this calcified structure is seen. However, bone is being deposited on it. E, normal cartilage shaft junction from the lower femur of a fourteen month old child (HLH 949, × 65). F, cartilage shaft junction of lower femur from a fourteen month old cretin (JHH 19962, × 65). Compare with E. Note absence of proliferative activity of cartilage cells, heavy calcification of matrix and dense bone without many osteoblasts.

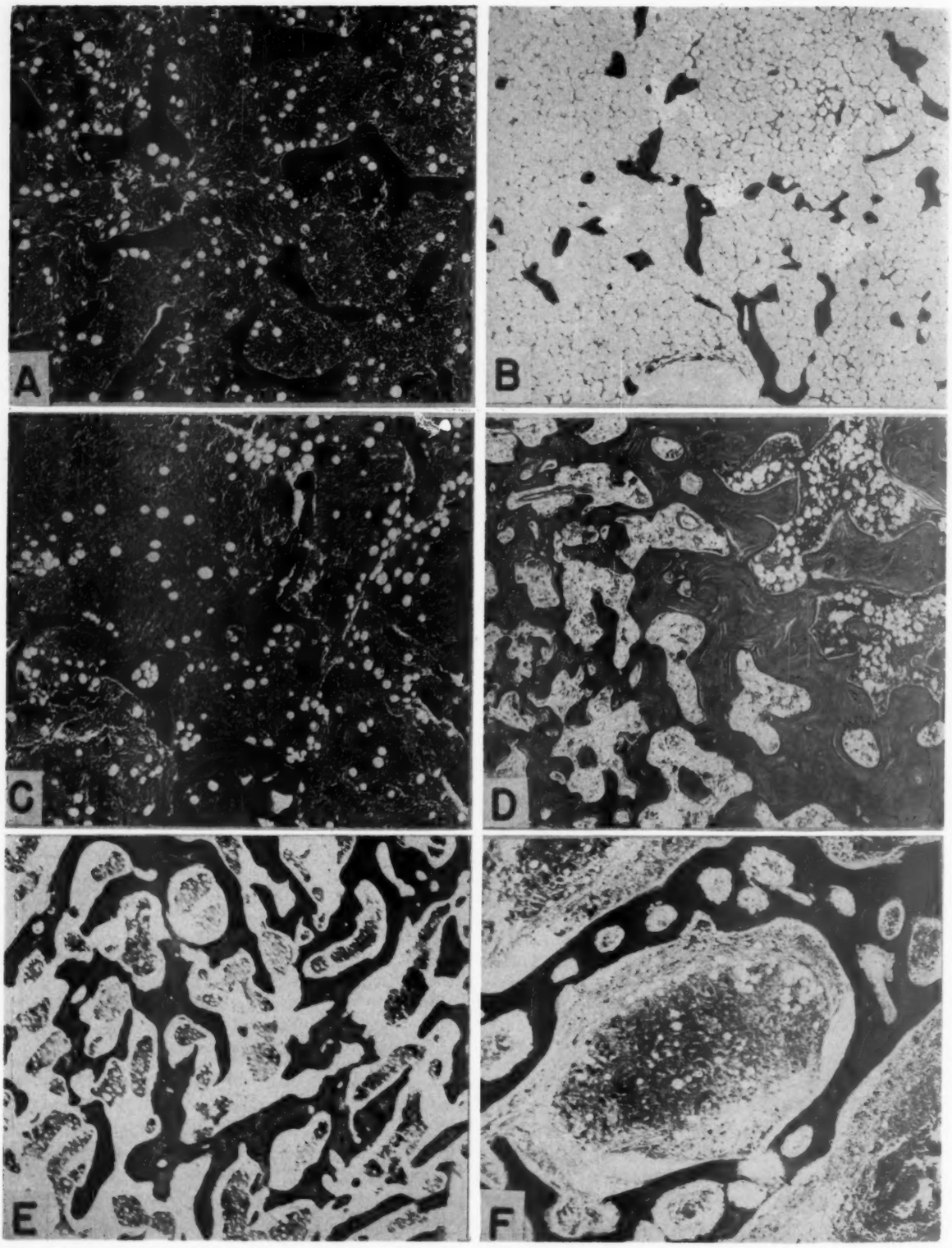

FIG. 4. (All magnifications are × 21.) A, normal vertebral body from a well nourished fifty-four year old Negro man dying suddenly as a result of skull fracture. Note approximate number and size of trabeculae (JHH 16358). B, Cushing's syndrome. Vertebral body from a thirty-nine year old woman with spontaneous fractures and all other manifestations of the disease. Note reduced number and size of trabeculae, together with fatty marrow (JHH 22939). C, senile osteoporo-

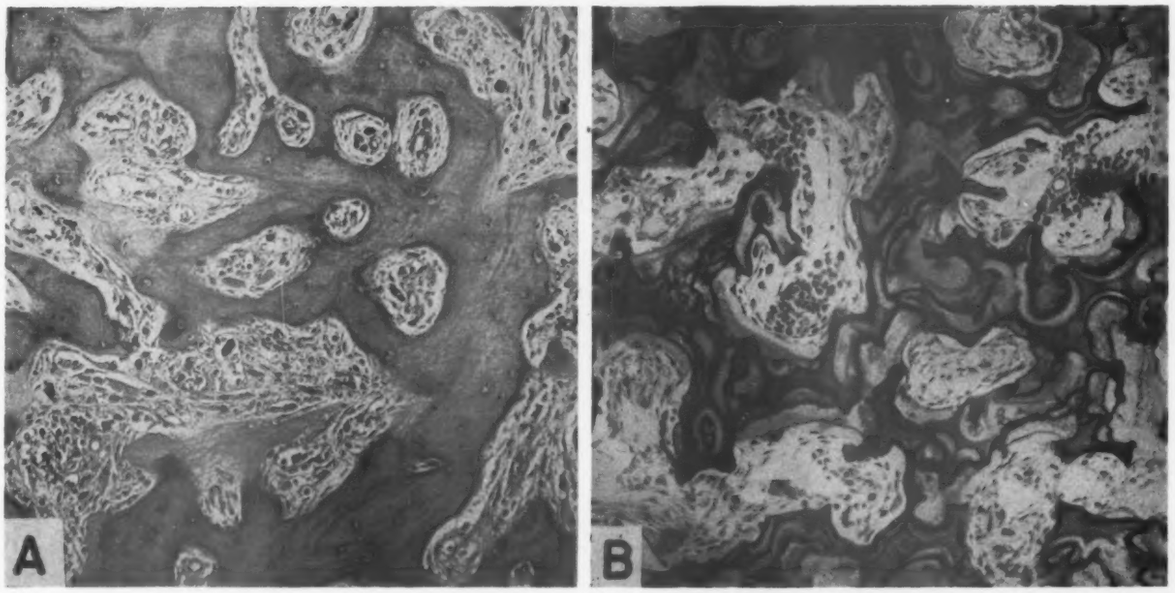

FIG. 5. A, vertebral body from a forty-six year old white woman exhibiting the clinical syndrome of osteomyelosclerosis (No. 2098, × 120). Note excessive bone and cellular marrow containing numerous megakaryocytes. Some of matrix formed by cells contains no inorganic materials. B, vertebral body from a four and one-half month old white boy dying with osteopetrosis (HLH 1565, × 120). Note dark cores of calcified cartilage matrix which has never been destroyed. This is covered with bone some of which shows osteoid borders. Marrow space is greatly reduced.

or is reduced, and osteoblastic activity continues, a stratum of bone may be deposited on the under surface of the cartilage. Then, when growth of the cartilage begins anew, a transverse stratum or "line" may be seen in the metaphysis by x-ray as the cartilage grows away from it [*19*]. In addition to dietary factors, circulatory defects are likewise of importance. Here immobilization may play a role [*20*].

Among endocrine disturbances those of the pituitary [*21*], thyroid [*22*] and adrenal [*23*] glands are prominent. The hypopituitary dwarf, the cretin and the infant with Cushing's syndrome all show reduction in the proliferative activity of the epiphyseal cartilage cells. It would be difficult to tell one from the other under the microscope.

DISTURBANCES IN THE OSTEOGENIC-OSTEOLYTIC BALANCE

The next important group of diseases are those associated with derangements in the equilibrium between bone formation (osteoblastic activity) and bone destruction (osteolytic activity). Imbalance of these two phenomena may lead to bones that are decreased or increased in density. Certain general terms, whose meaning must be clearly understood, are used to describe these changes. These terms are *osteoporosis*, *osteosclerosis* and *osteitis fibrosa*.

Osteoporosis (Figure 4) can be defined as any skeletal abnormality which is characterized microscopically by a decrease in the number and thickness of normally calcified trabeculae and in the amount of cortex present. Although such a change imparts the picture of rarefaction to the x-ray, the terms "decalcified" or "demineralized," which are so frequently employed by the roentgenologist, are not at all accurate. This is because the bone which is present contains a normal amount of inorganic material unless osteomalacia, too, is present.

Osteosclerosis (Figures 4 and 5) is the direct opposite of osteoporosis. In this state the bone is characterized by an increased number and the size of trabeculae and by an increased width of

sis. Vertebral body from a seventy-eight year old white woman who had spontaneous fractures. Note decrease in number of trabeculae (JHH 15314). D, Paget's disease. Vertebral body showing dense trabeculae with mosaic appearance and fibrous marrow. This bone proliferation completely obscures the primary change, osteitis fibrosa (see Figure 6F) (JHH 16975). E, osteosclerosis associated with metastatic carcinoma. Vertebral body from a man dying of carcinoma of prostate. Epithelial cells are found between dense trabeculae (JHH 17877). F, osteitis fibrosa associated with chronic renal disease. Vertebral body from a seventeen year old boy dying of chronic renal insufficiency. Secondary parathyroid hyperplasia was present. Note destruction of central portions of trabeculae and fibrous tissue about them (JHH 20502).

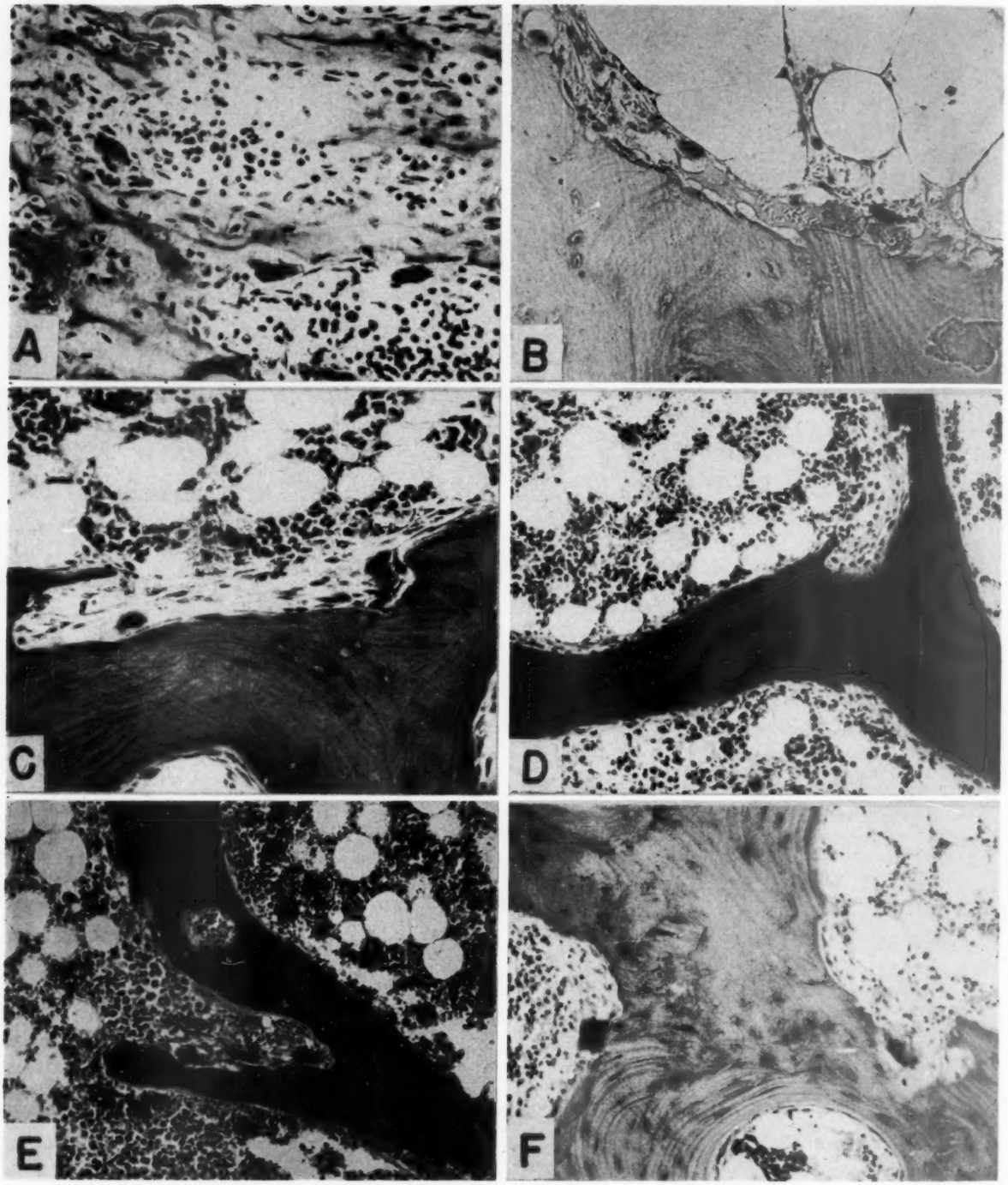

FIG. 6. A, excessive destruction in metaphysis. Rib from a six month child dying of neuroblastoma. Cellular activity has changed from construction to destruction as evidenced by osteoclasts (HLH 1186, × 200). B, primary hyperparathyroidism. Biopsy of clavicle at operation for removal of functioning parathyroid adenoma in a thirty-six year old man with hypercalcemia and hypophosphatemia (50-4693, × 200). C, secondary hyperparathyroidism. Section from vertebral body of a five year old child dying of chronic glomerulonephritis. Note excess destruction. (JHH 24065, × 200). D, secondary hyperparathyroidism. Section of vertebral body from adult dying of chronic pyelonephritis to show focus of destruction (JHH 16668, × 120). E, hyperthyroidism. Vertebral body from adult dying in postoperative "thyroid storm." Note focus of excess destruction (JHH 13821, × 120). F, Paget's disease. Several foci of destruction in vertebral body. These are early changes. Elsewhere the bone shows more classic alterations with increased density (see Fig. 4D; JHH 16975, × 120).

the cortex. On x-ray the bone is excessively dense.

Osteitis fibrosa (Figure 6) is a term which indicates increased destruction, evidenced by excessive osteolytic activity by osteoblasts and osteoclasts. As we shall see, a number of metabolic disturbances may lead to the picture of osteitis fibrosa.

The first main category (Table II) in this group of diseases is "Decreased Osteoblastic Activity" Such a disturbance leads to the picture of osteoporosis. A number of factors may be in operation, whether one is dealing with the rapidly growing skeleton of the child or the more slowly growing bone of the adult. In either case, the end result, a rarefied structure, is the same. It is unnecessary to mention here all the diseases listed in Table II. The fundamental disturbance concerns the osteoblast and its product, osteoid. Either the cell is unable to function or else the building blocks necessary to form its product are insufficient. The chemical sequences associated with matrix formation in the normal organism are unknown. Hence we can only cite certain factors which are of consequence. Physical agents such as various types of radiation are important [*17*]. Genetic factors appear to account for the defects in collagen formation in the corium, sclera, teeth and bone which characterize the osteogenesis imperfecta syndrome [*24*]. In this condition, at least in certain cases, the maturation of collagen may be at fault.

Nutrition plays an extremely significant role with regard to the functional integrity of the osteoblast [*18*]. Not only calories, but all the essential nutrients: elements, amino acids, vitamins and fatty acids, are of importance. With certain exceptions, cartilage is equally susceptible. Deficiency of ascorbic acid [*25*] exhibits a rather unique pattern which somewhat resembles that which is seen in the osteogenesis imperfecta syndrome. Cartilage growth goes on in fairly normal fashion while the activity of the osteoblast is greatly impaired. The pediatrician is familiar enough with the rarefaction of the shaft of long bones which is encountered in scorbutic children.

Certain local disturbances of the nutrition of the osteoblast must be mentioned. Impairment of the blood supply, particularly as a result of disuse, would appear to favor a reduction in osteoblastic activity [*26*]. Since the bony area in question becomes rarefied, one would expect that normal destructive phenomena are occurring.

TABLE II

DISTURBANCES IN OSTEOGENIC-OSTEOLYTIC BALANCE

A. Decreased Osteoblastic Activity (Osteoporosis)
Genetic:
Osteogenesis imperfecta syndrome [*24*]
Ehlers-Danlos syndrome [*40*]
Physical:
Radiation [*17*]
Nutritional:
Lack of essential nutrients, dietary or conditioned [*18*]
and, in particular, ascorbic acid [*25*]
Immobilization or disuse [*26*]
Endocrine:
Hypopituitarism [*21*]
Hypothyroidism [*22*]
Cushing's syndrome [*23*]
Postmenopausal osteoporosis [*27*]
Miscellaneous:
Idiopathic osteoporosis [*27*]
Tumor cells in marrow [*29*]
B. Increased Osteoblastic Activity (Osteosclerosis)
Genetic:
Osteopathia striata [*30*]
Osteopoikilosis [*31*]
Physical:
Radiation [*32*]
Trauma [*40*]
Endocrine:
Hyperpituitarism [*33*]
Miscellaneous:
Fluorosis [*34*]
Vitamin A intoxication [*35*]
Hypertrophic osteoarthropathy [*36*]
Osteosclerosis [*37*]
Progressive diaphyseal dysplasia [*38*]
Melorheostosis [*39*]
Metastatic tumors [*40*]
C. Decreased Osteolytic Activity (Osteosclerosis)
Genetic:
Osteopetrosis [*41*]
Miscellaneous:
Erythroblastosis fetalis [*42*]
Heavy metal deposition
Lead [*43*]
Bismuth [*44*]
D. Increased Osteolytic Activity (Osteitis Fibrosa)
Nutritional:
Severe inanition [*41*]
Endocrine:
Hyperparathyroidism
(1) Primary [*27,48*]
(2) Secondary [*49, 55*]
Hyperthyroidism [*50,51*]
Miscellaneous:
Paget's disease [*52*]
Metastatic tumors [*40*]

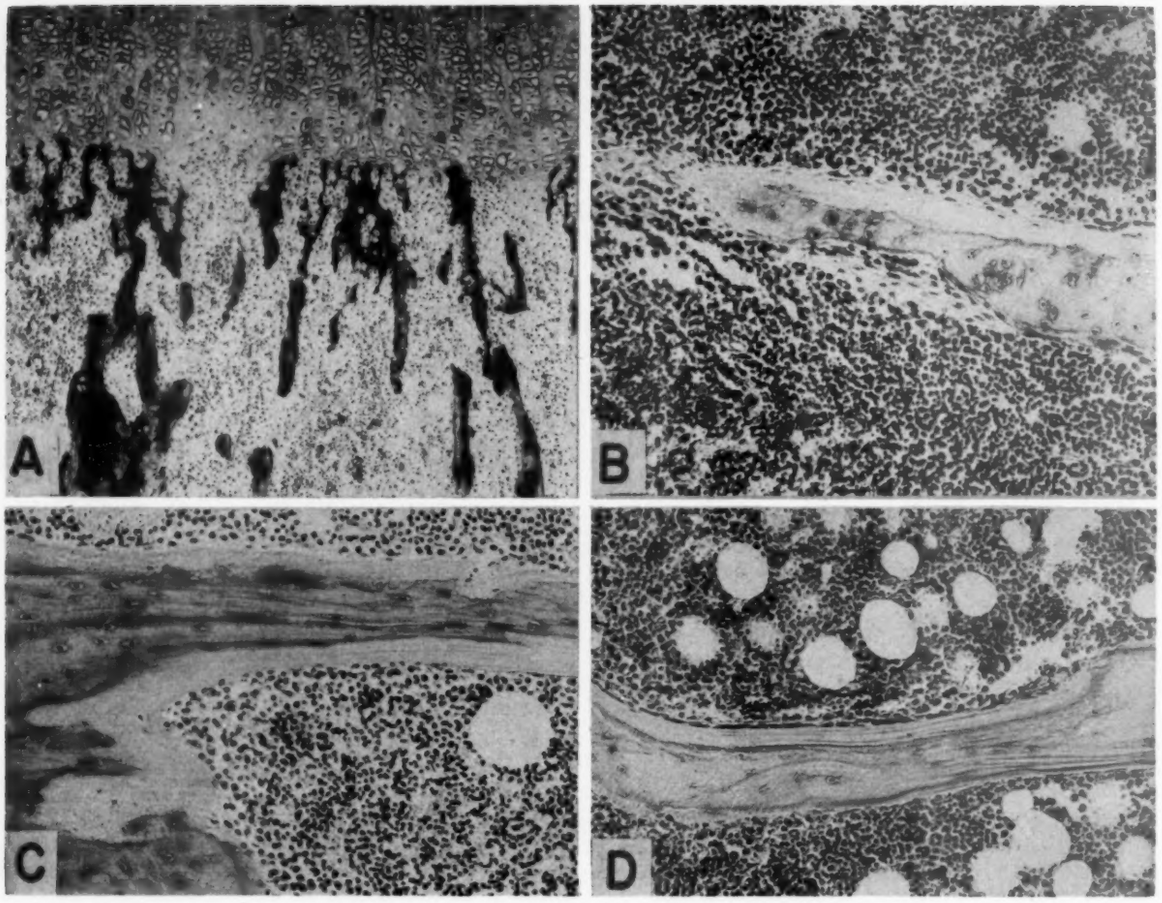

FIG. 7. A, rickets, severe. Costochondral junction from a two and one-half month old infant dying with diarrhea. Vitamin D had never been administered. Note extensive defects in deposition of inorganic salts in cartilage matrix (HLH 1174, × 50). B, rickets. Trabeculae from shaft of rib in a seven months old infant dying of lobular pneumonia. Upper surface is covered by osteoid. Lower surface has focus of destruction, as in osteitis fibrosa (HLH 1112, × 120). C, rickets associated with renal disease in a child. Wide borders of osteoid are clearly seen (JHH 23051, × 120). D, rickets associated with renal disease in an adult. Again a wide zone of osteoid is present (JHH 16067, × 120).

Among endocrine dysfunctions, Cushing's syndrome furnishes the most striking example of the effects of decreased osteoblastic activity in the child or adult [*23*]. In this disease the trabeculae are thin and decreased in number. From this picture, one infers that the osteoblast is at fault. No evidence of excess destructive activity is present. The exact pathogenesis of this change is not clear, although it has been produced as a result of adrenal cortical hormone administration. Other endocrine disturbances affect osteoblastic activity. Osteoporosis is seen in the hypopituitary [*27*] as well as in the hypothyroid state [*22*]. Deranged ovarian function may also lead to osteoporosis of the so-called postmenopausal type [*27*]. Estrogen therapy certainly affects the well-being of such patients. The osteoporosis which is said to be encountered in some cases of acromegaly [*27*] is difficult to explain. One wonders if it may be related to the severe joint changes which may be such a conspicuous part of this syndrome [*28*] and which might lead to rarefaction from disuse.

Finally, decreased bone density may be seen when large numbers of adventitious cells (leukemia, myeloma, carcinoma, and the like) are present in the marrow spaces [*29*]. Under such circumstances there need be no evidence of excess destruction. As usual, there is always an idiopathic group [*27*] and the less said about this the better.

The antithesis of osteoporosis is osteosclerosis, that is, bone which is composed of more numerous and thicker trabeculae. Such a disturbance may come about in two principal ways: (1) increased osteoblastic activity (with normal

osteolytic function) and (2) decreased osteolytic activity (with normal or even decreased osteoblastic function). It is usually not difficult to differentiate these two types of abnormality. (Table II, B and C.)

Certain genetic disturbances such as osteopathia striata [*30*] and osteopoikilosis [*31*] are poorly understood. Radiation may lead to excess bone formation; this depends on the dosage and doubtless other unknown factors [*32*]. Particularly prominent is the sclerosis accompanying the deposition of certain radioactive elements. The endocrine disturbance, acromegaly, which is caused by excessive production of growth hormone by a pituitary tumor, is the classic example of excess bone formation [*33*].

When large amounts of fluoride enter the body as a result of inhalation or ingestion, dense bone is found. This is produced by excessive osteoblastic activity [*34*]. A proliferation of bone cells may also be encountered when toxic doses of vitamin A are administered [*35*].

A large number of miscellaneous conditions [*36–39*] also must be mentioned, since osteoblastic activity appears to be excessive. We know so little about them that we can only give their names and, in embarrassment, go on to the next group which is characterized by decreased osteolytic activity.

If virtually all the bone formed at the cartilage-shaft junction were not removed, an inordinately dense structure devoid of marrow spaces would result. This is exactly what happens in osteopetrosis or marble bone disease [*41*]. The characteristic pathologic change in this condition is a bone made up of trabeculae which contain large amounts of calcified cartilage matrix material encased in bone. Some of the latter is poorly calcified, that is, rickets is also present. Relatively little destructive activity is apparent. In fact, osteoclasts are usually seen only in areas where fractures have occurred. Osteopetrosis is a hereditary disturbance which is, of course, of serious consequence because of its effects on blood cell formation. The presence of extraneous elements such as lead [*43*] or bismuth [*44*] may lead to localized areas of sclerosis, the cause of which appears to be defective destruction.

The last of the four types of bone disease in this group is characterized by excess destruction. To this the term, *osteitis fibrosa*, may be applied. Osteitis fibrosa, or more correctly ostitis fibrosa, was the term used by von Recklinghausen in 1891 [*45*] to describe a series of patients exhibiting severe bone rarefaction. One of these patients had hyperthyroidism. At least one other probably had a parathyroid tumor, although the relationship of this type of neoplasia to bone disease was not clearly demonstrated until some thirty years later.

Today, the term, osteitis fibrosa, has come to be used whenever the picture of excess bone destruction is present. Such evidence consists of eroded, saw-tooth trabeculae or lacunar foci containing osteoclasts and connective tissue cells. Another prominent part of the picture is the presence of intratrabecular destruction, such as vascular channels and cells which seem to be eroding the trabeculae from within. The stimuli for destruction are not entirely clear, although two mechanisms may be mentioned. The parathyroid hormone appears to have a direct action on bone destruction [*47*]. Another stimulus to the destructive activity by bone cells is mediated via the humoral concentrations of calcium and phosphorus in the plasma, which are mediated by the parathyroid glands [*46*], together with changes in intake or excessive losses of these two elements.

Primary hyperparathyroidism may be accompanied by skeletal disease [*27*] although this is not an invariable consequence. The histologic changes in the skeleton may be slight or extensive. Similar bone lesions are seen in persons dying as a result of chronic renal insufficiency of varying types. It is generally assumed that hypocalcemia is the stimulus to parathyroid overactivity which then leads to osteitis fibrosa.

An identical picture may be seen in cases of severe hyperthyroidism, in which balance studies [*50*] appear to explain the excess destruction [*51*].

The primary defect in Paget's disease consists of localized foci of excess destruction. The excess proliferation which appears later to dominate the picture is assumed to be secondary [*52*].

DISTURBANCES IN THE DEPOSITION OF HYDROXYAPATITE IN CARTILAGE MATRIX AND/OR OSTEOID

The last group of diseases which we have to discuss are those characterized by a decreased content of bone salt (hydroxyapatite) in the matrices of cartilage and/or bone. The term *rickets* is used to designate this situation in the growing individual; hence cartilage and bone are

usually both involved. In the adult, the term *osteomalacia* indicates a reduced amount of inorganic material in bone matrix (osteoid). Rickets and osteomalacia may be diagnosed most precisely either chemically or microscopically. By chemical analysis a specimen of dry, fat and marrow-free bone from a normal person is found to have an inorganic content (ash) of about 60 per cent. The lower limit of normal has never been specifically set; values below 50 per cent might be taken to indicate that rickets or osteomalacia is definitely present. If one searches under the microscope for areas of cartilage or bone matrix devoid of mineral, the diagnosis can easily be made anatomically.

TABLE III
DISTURBANCES IN DEPOSITION OF HYDROXYAPATITE IN CARTILAGE MATRIX AND/OR OSTEOID (RICKETS OR OSTEOMALACIA)

A. Disturbance in Balance of Matrix Production and Deposition of Hydroxyapatite
Rapid matrix formation, particularly in the premature infant [*53*]
Healing fractures [*54*]
Healing scurvy [*25*]
Healing bone following removal of parathyroid tumor [*27*]
B. Disturbance in Intestinal Absorption of Calcium and/or Phosphorus
Calcium
Dietary lack [*56*]
Change in pH of intestinal contents [*57*]
Formation of insoluble complexes: oxalate [*58*], phytin [*59*]
Protein content of diet [*60*]
Steatorrhea, sprue [*61–63*]
Vitamin D lack
Dietary [*64*]
Steatorrhea [*61–63*]
Absence of bile [*65*]
Absence of pancreatic juice [*66*]
Impaired formation in skin [*67*]
Phosphorus
Dietary lack
Change in pH of intestinal contents [*57*]
Steatorrhea [*61–63*]
Formation of insoluble complexes
C. Excess Excretion of Calcium and/or Phosphorus
Renal Disease
Glomerulo-tubular [*49,55,68*]
Tubular (frequently hereditary) [*69–72*]
"Phosphate diabetes"
"Phosphate diabetes" with glucosuria
Fanconi syndrome (phosphaturia, glucosuria, amino aciduria)
Renal tubular acidosis [*73*]
Idiopathic hypercalciuria [*27*]
Pregnancy; lactation [*63*]
D. Obscure
Hypophosphatasia syndrome [*74*]

Certain concentrations of calcium and phosphorus must be present in interstitial fluids if hydroxyapatite is to be deposited in the organic matrices of cartilage and bone. The exact mechanism which is involved is unknown. There is, of course, a delicate balance between the formation of matrix and its mineralization. It is likely that the matrix must be in a certain state of "maturity" to be calcifiable. Moreover, certain situations may alter the serum levels of calcium and phosphorus so as to lead to decreased deposition of hydroxyapatite in cartilage and bone. These are grouped in Table III.

In some circumstances matrix production may be excessive. As a result, even though the concentrations of calcium and phosphorus, as mirrored by serum levels, seem optimal, deposition of inorganic salts does not keep pace. Rickets or osteomalacia is then to be found. (Table III.) For instance, the rapidly growing infant, particularly the premature infant, exhibits zones of osteoid which may be in excess of what one would wish to call "physiologic" [*53*]. The callus of a healing fracture also shows similar areas of newly-formed uncalcified matrix [*54*]. In this situation the matrix itself may not be mature enough for calcification to take place. A similar state is encountered in healing scurvy, where incipient rickets may be brought out as a result of excessive osteoid formation [*25*]. The bones of persons from whom a parathyroid tumor has recently been removed may show an overabundance of newly-formed bone matrix [*27*]. Here, of course, lately altered serum levels may reflect non-optimal concentrations for calcification to take place. A last example to deserve mention is osteopetrosis (marble bone disease). In this disease, normal destructive activity is impaired or even completely lacking. Hence large amounts of ordinarily available calcium and phosphorus are "locked up" in the skeleton and are not available for normal redistribution. In our experience, marble bone disease is usually accompanied by rickets [*41*].

A large number of factors may affect the ab-

sorption of calcium and/or phosphorus from the intestinal tract. (Table III.) With respect to calcium, dietary restriction is of importance [*56*], although in man uncomplicated calcium deficiency must be most uncommon. Calcium absorption is affected by the pH of the intestinal contents; acidity facilitates, while alkalinity inhibits calcium uptake [*57*]. Any number of acidic radicles may form insoluble complexes with calcium; such include oxalate (spinach) [*58*] and, particularly, phytate [*59*]. The latter is of importance with respect to cereal grains in which it is found in large amounts. The protein content of the diet affects the absorption of calcium; a high intake promotes an increase, and conversely [*60*]. Large losses of calcium from the intestine may result from diarrhea, particularly in the sprue syndrome [*61*] and in idiopathic steatorrhea [*62,63*]. The latter disease state may be present without any clinical evidence of deranged intestinal function.

The dietary intake of vitamin D is of the utmost importance to the growing child as far as calcium uptake is concerned [*64*]. The absorption of vitamin D may be impaired by a variety of circumstances. Syndromes such as sprue and steatorrhea, which interfere with the absorption of lipids, depress the uptake of vitamin D. Since bile and pancreatic secretions are also of importance in this respect, rickets is seen in children with congenital atresia of the bile ducts [*65*], and in cystic fibrosis of the pancreas [*66*].

Of the disturbances in excretory function (Table III) which may affect the metabolism of calcium and/or phosphorus, those which are associated with chronic glomerulo-tubular disease are the most common [*49,55*]. The three most prevalent forms of chronic nephritis are vascular, glomerular and pyelonephritis. Two changes in the bones are prominent: excessive destructive activity (osteitis fibrosa) and the presence of excess osteoid (rickets or osteomalacia). These alterations were explained by Albright and Reifenstein [*27*] as follows. Tubular disease leads to acidosis which is followed by hypercalciuria and hypocalcemia. The latter gives rise to parathyroid hyperplasia, which is ineffective as far as phosphate excretion is concerned. Hypocalcemia and hyperphosphatemia are the rule; the latter is due to tubular dysfunction. Even though the product of the serum concentrations of calcium and phosphorus is high, excess osteoid is seen. The reason for this is not entirely clear [*68*]. The excess destruction (osteitis fibrosa) which is observed has been ascribed to parathyroid stimulation.

In recent years an increasing number of isolated renal tubular defects have come to be recognized. These are associated with an inability to resorb certain metabolites such as water, phosphate, glucose, cystine and other amino acids, calcium, bicarbonate, potassium and sodium from the glomerular filtrate [*69*]. Certain of these defects may lead to rickets or osteomalacia.

The most important is a syndrome sometimes having an hereditary background, which makes its appearance in childhood or in early adulthood [*70–72*]. It has received a number of names; "vitamin D resistant rickets" and "phosphate diabetes" have been the most widely used. As might be expected, rickets is present. Serum calcium values are usually normal; hypophosphatemia is the rule. Hyperphosphaturia is present in those cases in which this aspect has been studied. Large amounts of vitamin D, so large as to be in the toxic category, usually are effective. This response has led to the term, "vitamin D resistant rickets." It is not clear, however, exactly how the vitamin acts when it is effective. If one believes that vitamin D has a specific effect on the resorption of phosphate, the observed therapeutic effect makes some sense. On the other hand if one does not accept the evidence for a primary action of vitamin D on the function of the kidney tubule, he is left with the feeling that the phosphate diabetes is being helped, although, of course, not always, by toxic amounts of vitamin D operating in an unexplained fashion. We would prefer the term, phosphate diabetes, as do others, and look at the disease as a specific tubular defect unrelated to vitamin D.

Several other closely allied syndromes are seen, in all of which rickets or osteomalacia are present. The phosphaturia just mentioned may be accompanied by glucosuria. In other cases amino aciduria with or without loss of potassium, and sometimes defective acidification of the urine is observed; these fall into the designation of "Fanconi syndrome."

The renal acidosis syndrome [*73*] must be looked upon as another primary disturbance of the renal tubule. This is seen in infants, adolescents or adults and may have a familial incidence. Metabolically, the primary disturbance appears to be an inability to produce a urine of normal acidity. The urine, which is of increased volume, is alkaline, with fixed specific gravity.

Acid metabolites are excreted with fixed base, so that a constant loss of sodium, potassium and calcium occurs. The acidosis is characterized by low plasma bicarbonate, increased plasma chloride and decreased plasma inorganic phosphorus levels. There is frequently nephrocalcinosis. Rickets or osteomalacia is present. Weakness as a result of hypokalemia may be prominent.

The syndrome of "idiopathic hypercalciuria" [*27*] is poorly understood. It is separated from the primary tubular disorders already cited by the absence of acidosis. These persons have osteomalacia; their main difficulty, however, is renal calculi.

The newly-described syndrome of hypophosphatasia is characterized by rickets, together with hypercalcemia, sometimes hyperphosphatemia and, of course, a decrease in serum alkaline phosphatase activity [*74*]. This biochemical picture is also reminiscent of what is seen in hypervitaminosis D in children [*75*].

Despite the large number of disease syndromes to which we have referred so briefly, and despite the others which are noted in Tables I, II and III, the anatomic changes which are found in the cartilage and/or bone are really not particularly complex. They are merely exaggerations of the normal pattern in terms of too little or too much.

In the case of cartilage, the fundamental change is one of varying degrees of chondrodysplasia, with the main emphasis on too little. In this group are found minimal degrees of growth arrest which may be followed as they increase in severity to the marked alterations encountered in chondrodystrophy and the endocrinopathies. Decrease in the inorganic content of the cartilage characterizes rickets.

In the case of bone, one is also confronted with the problem of too little or too much, in the inorganic content of osteoid as well. If the bone is rarefied, one may be dealing with decreased osteoblastic activity or with excessive destructive processes. If the bone is too dense, osteoblastic activity may be excessive or destructive sequences can be retarded.

The more complex anatomic pictures merely include several alterations occurring together, such as chondrodysplasia and osteoporosis in Cushing's syndrome in infants; rickets or osteomalacia and osteitis fibrosa in chronic renal disease of children or adults; rickets and decreased destruction in osteopetrosis; and osteitis fibrosa sometimes with osteomalacia, in hyperthyroidism. Again, however, the morphologic alterations are stereotyped. Bone is no exception to the dictum that tissue changes are not necessarily specific for a given disease. Despite this, even today, bone biopsy may be of help in elucidating the nature of some complex clinical problems in which the skeleton may be involved.

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Clinico-pathologic Conference

Sore Mouth, Purpura, Weight Loss, Hepatomegaly, Peripheral Neuritis and Monocytosis

STENOGRAPHIC reports, edited by Lillian Recant, M.D. and W. Stanley Hartroft, M.D., of weekly clinico-pathologic conferences held in the Barnes and Wohl Hospitals, are published in each issue of the Journal. These conferences are participated in jointly by members of the Departments of Internal Medicine and Pathology of the Washington University School of Medicine and by Junior and Senior medical students.

THIS eighty-two year old white man (No. 271799) was admitted to the Ear, Nose and Throat Service of the McMillan Hospital for the first time on May 10, 1956, with the chief complaint of a sore mouth for ten months. He was subsequently transferred to Barnes Hospital and died July 10, 1956.

The patient was in excellent health until eight years before admission when he had to stop work because of the development of dyspnea on exertion. Otherwise he remained well until two years before admission when he noted a crusted area on the hypothenar area of the right hand which he trimmed periodically with a knife. He had been weak and easily fatigued for the year before admission. During this time his gait was unsteady but was not made worse by walking in the dark. Ten months before admission pain developed in his gums and buccal mucosa especially when eating. This pain was attributed to dentures, although he had worn the same dentures for many years previously without difficulty. The pain was not worse when the dentures were in place. Local therapy was ineffective. Despite occasional remissions there was a progression of the soreness until it involved the entire mouth. From this time until admission he suffered a 40 pound weight loss which he attributed to a decreased food intake because of pain on chewing. Five months before admission, increasing dyspnea on exertion limited his walking to one-half to one block. A mild non-productive cough developed. There was no orthopnea, nocturnal dyspnea or chest pain. At this time he received seventeen injections in the hip. Following these injections a drop foot developed on the left foot. Specific questioning elicited the facts that he had been a pipe smoker for sixty-five years; that he drank water from a 32 foot well located 20 feet from an outside toilet; that he had not recently been exposed to animals or to fowl excreta; and that he had been exposed to metal dust over a five year period while engaged in the occupation of filing saws.

Review of the past history was negative except for the following: The patient had undergone a cataract extraction five years before admission and a herniorrhaphy thirty-one years before admission. His urinary stream had been narrow for five years and there was an associated mild urinary frequency. The patient's father had suffered from pulmonary disease of unknown type.

On physical examination the temperature was 37.2°C., the pulse 96, respirations 20, and the blood pressure 125/75. The patient was well developed and well nourished and did not appear ill. The skin had a lemon yellow tint. There was a crusted 1 by 2 cm. area on the hypothenar eminence of the right hand. Petechiae were scattered over both flanks. An operative defect was noted in the left iris. The right fundus showed arteriosclerosis of the vessels. The left fundus was not well visualized. There was some crusted blood on Little's area on the right. The nasopharynx was clear. The surface of the upper and lower gums was granular, rough and ulcerated. This lesion extended over the hard palate, the buccal surface of the cheeks and the floor of the mouth. The entire area showed telangiectasia and dilated blood vessels. The dorsum and sides of the tongue were covered with a

thick yellow-white exudate. The lesions were slightly sensitive to touch. The pharynx and hypopharynx were normal. There was no lymphadenopathy. The chest was hyperresonant and clear to auscultation. The heart was enlarged to the left with a totally irregular rhythm. The liver edge was felt at the costal margin. Bilateral direct inguinal hernias were present. The prostate was small. There was 2+ ankle edema. Posterior tibial pulses were not palpable. The dorsalis pedis pulses were weak bilaterally. Neurologic examination demonstrated considerable weakness of the dorsiflexors of the feet and toes, impaired position and vibration sense in the lower extremities and absent ankle jerks. The patient tended to pitch forward when walking. The Romberg test was positive.

Laboratory examinations revealed the following: Hemoglobin 14.5 gm./100 ml., white blood count 8,750 cells per cu. mm., 61 per cent segmented forms and 39 per cent lymphocytes. Red blood cells and platelets appeared normal on smear. The urinalysis was normal with a specific gravity of 1.020 and 0 to 1 white blood cells in the spun sediment. The packed red cell volume was 47 per cent and the actual sedimentation index was 17 mm./hr. The cardiolipin reaction was negative on three occasions. The serum sodium was 143 mEq./L., potassium 5.3 mEq./L., total protein 6.6 gm./100 ml., albumin 3.0 gm./100 ml., globulin 3.6 gm./100 ml.; bromsulphalein 33 per cent retention in forty-five minutes, prothrombin time seventeen seconds with a control of fourteen seconds, cephalin cholesterol flocculation test 2+, thymol turbidity 1.6 units, alkaline phosphatase 2.8 Bodansky units, cholesterol 96 mg./100 ml., protein bound iodine 4.2 gamma/100 ml. and the total bilirubin was less than 0.8 mg./100 ml. Four stools were guaiac negative and one stool showed a trace positive. Culture of the oral lesion grew out Neisseria, Alkaligenes fecalis, Staphlococcus albus, alpha streptococcus and a moderate number of organisms reported as probably Hemophilus. Cultures for fungus were reported as "no growth." The first strength PPD was equivocal, the intermediate strength was negative. A histoplasmin skin test was positive. A skin test with old tuberculin was negative. Roentgenograms of the chest showed cardiac enlargement and pulmonary vascular engorgement. There was a nodular infiltration throughout both lung fields. Bilateral pleural effusions were present. Intravenous pyelograms were within normal limits. An electrocardiogram showed changes compatible with an old anteroseptal myocardial infarction and auricular fibrillation. Roentgenograms of the lumbar spine showed a narrowed fourth lumbar intervertebral disc space with questionable spondylolisthesis of L4 on L5 with hypertrophic degenerative changes of the dorsal and lumbar spine.

On May 15, 1956, a diagnosis of cardiac insufficiency was made by a medical consultant. The patient had fine rales at both lung bases with impaired resonance at the left base. The liver was felt three fingerbreadths below the right costal margin and the spleen one fingerbreadth below the left costal margin. The circulation time was twenty seconds (decholin®) and Rumpel-Leeds test was negative. The patient was started on digitalis on which he remained with resultant weight loss of 14 pounds and a decrease in cardiac size. On May 20, 1956, the patient was transferred to the Medical Service where he remained until June 24, 1956. During this time he had an intermittent fever with periods of normal temperature which persisted as long as one week and febrile episodes lasting from seven to ten days. Daily maximum temperatures reached 39°C. Three blood cultures taken during febrile episodes did not yield any growth. The patient was given a trial of therapy with achromycin® 250 mg. every eight hours for eight days without noticeable effect, although he was afebrile during the last four days of therapy. He also received a multivitamin preparation throughout his hospital stay. Petechiae which had been noted in the flanks at admission, spread and coalesced to involve the lateral aspect of the chest and the lateral aspect of the buttocks.

Laboratory examinations at this time revealed the following: Hemoglobin 17.5 gm. per cent, reticulocytes 2.1 per cent, white blood count 12,500 cells per cu. mm. with 1 per cent juvenile forms, 2 per cent stabs, 61 per cent segmented forms, 20 per cent lymphocytes and 16 per cent monocytes. Many of the monocytes were young looking. There was 1+ aniso and poikilocytosis. There were 107 platelets per 1,000 red blood cells. Two bone marrow examinations were performed. The marrow was cellular with a slight increase in plasma cells, reticulum cells and monocytes. There was a shift to younger forms in the granulocytes. The erythroid series and megakaryocytes were normal. Cultures of the bone marrow for bacteria and fungi were

sterile. The white blood cell count throughout this period ranged from 8,000 to 12,000 with monocytes from 13 to 27 per cent of the total differential.

A lumbar puncture was performed. The initial pressure was 150 mm. of cerebral spinal fluid. There were no cells and protein was 83 mg. per cent. Serology and colloidal gold were negative. The umbilical reflexes, knee and ankle jerks were absent. Bilateral foot drop and calf fasciculations associated with impairment of position and vibration sense in the feet were also noted. It was the opinion of the neurologist that the patient was suffering from a dorsal root radiculopathy or a peripheral neuropathy.

Biopsy specimens were taken from many sites. Biopsy of the oral lesion showed chronic inflammation with a predominantly histiocytic response. No giant cells and no organisms were seen. The inflammatory response was thought to be suggestive of histoplasmosis. The sections were interpreted as chronic inflammation. Repeat biopsies from three sites in the oral cavity showed essentially the same findings with the same interpretation. Fungus culture of the biopsy material yielded no growth. Biopsy of a petechial area of the skin showed only focal hemorrhage and perivascular infiltration largely of lymphocytes and histiocytes. No vasculitis or necrosis was seen. An observer felt that there was fixation of the rectum secondary to tumor. Sigmoidoscopic examination was not revealing except for an adenomatous polyp which was biopsied. The urologic consultant inserted a biopsy needle into what was felt to be an anterior rectal mass and also into the prostate. Sections showed only striated muscle, blood vessels and fibrous connective tissue. A gastrointestinal series showed a duodenal deformity without demonstrable ulcer crater. There was some question of antral gastritis. Repeat gastric fillup was interpreted as antral gastritis and a duodenal deformity. Gastroscopy was not done because of the patient's poor general condition.

On June 24, 1956, the patient complained of a painful right leg which on examination was found to be cold, cyanotic and pulseless below the knee. Those in attendance believed he had probably had an embolus from the fibrillating auricle, occluding the superficial femoral artery. The decision to operate was made. Arteriosclerotic thrombosis of the superficial femoral artery was found. A thromboendarterectomy was performed and flow was reestablished. However, postoperatively the blood supply to the lower leg was inadequate. On June 27, 1956, a right mid-thigh amputation was found to be necessary. The patient tolerated the procedure well. Wound healing progressed slowly but definitely. On July 6, 1956, a low grade fever developed. On July 9, 1956, the blood pressure was found to be 70/30. Arterial insufficiency of the left lower leg was developing. The patient became obtunded and died several hours later.

CLINICAL DISCUSSION

DR. EDWARD REINHARD: This was a very complex case. The patient was an eighty-two year old man who presented with a sore mouth, dyspnea, cough, weight loss and an unsteady gait. On physical examination he was intermittently febrile and had a striking lesion involving his mouth and gums, a crusted lesion on his hand, hepatomegaly and extensive hemorrhagic skin changes. He was fibrillating and had edema of the ankles. A rectal shelf was described. From the mass of laboratory data, one is struck by the persistent monocytosis and the abnormal liver chemistries. It is stated in the protocol that the patient had had seventeen hip injections and it was implied that this was about five or six months before admission to the hospital. However there is one very specific note in the chart to the effect that these seventeen hip injections were given one year prior to admission to the hospital or before the onset of the sore mouth and gums. Let us start our discussion of this problem by viewing the x-rays.

DR. HARVEY A. HUMPHREY: The patient had an examination of the skull. No abnormality was seen and the sella turcica was normal in size and shape. No intracranial calcification and nothing suggesting increased intracranial pressure was noted. The initial examination of the chest shortly after admission revealed that the heart was somewhat enlarged. In addition there was an increase in the reticular pattern of the lung which was interpreted as pulmonary vascular congestion. The costophrenic angles were slightly blunted, probably due to a trace of fluid in each pleural space. Four days later there had been a perceptible diminution in the size of the heart and the lungs were definitely clearer. However, throughout each lower lobe, slight linear and nodular densities were seen which were thought to represent fibrosis, not of an unusual degree for this age. A follow-up examination on June 11,

the two previous ones having been made May 14 and 18, revealed no obvious changes. The fibrosis in each of the lungs persisted and the heart remained slightly enlarged. The interpretation was congestive heart failure with interval improvement. The dorsal and lumbar spine were examined and degenerative arthritis of a degree not particularly unusual for this age was seen. Evidence was found of considerable calcification of the aorta which appeared to taper down somewhat at the level of the bifiurcation. The abdomen was also examined and no calcification in the region of the adrenals was seen.

DR. REINHARD: Dr. Humphrey, was there any evidence in these films of heavy metal therapy?

DR. HUMPHREY: No. We did not see any evidence of heavy metal in the hips. Pyelograms showed the kidneys to be normal in size. A very faint concentration of dye was seen. This indicated that either the patient had not been dehydrated sufficiently or that some impairment of renal function existed. Radiologic examinations of the stomach were performed twice and were somewhat perplexing. Initially, the antrum appeared somewhat distorted with limitation in distensibility and slight thickening of the mucosal folds. In addition a deformity of the distal portion of the duodenal bulb was seen. That was thought to be due to peptic disease, namely an antral gastritis, probably with a duodenal deformity secondary to a previous duodenal ulcer. There was no evidence of an ulcer crater demonstrated on any of our two examinations. The colon was examined and no evidence of an intraluminal lesion was noted. We saw no evidence of the mass that had been palpated by digital examination of the rectum.

DR. REINHARD: Thank you Dr. Humphrey. Presumably because of the diagnostic difficulties, this patient had numerous biopsies. We have six pages of descriptive material covering the various biopsies that were performed. Dr. McGavran, will you discuss the biopsy sections?

DR. MALCOLM MCGAVRAN: As Dr. Reinhard has said we did receive an adequate number of biopsy specimens. Two biopsies of the gingiva and oral lesions were made. These revealed upon review a histiocytic response presumed to be due to a chronic inflammatory process. Examination even with special stains did not disclose any microorganisms. A biopsy of the iliac bone marrow was performed. Two minute clumps of bone marrow cells and lakes of red cells were seen. One of these clumps consisted of a homogeneous group of large pale eosinophilic, finely vacuolated, reticulum cells. A biopsy of the skin revealed purpura. A biopsy of the rectum revealed an adenomatous polyp, and the needle biopsy of the prostate and pelvic tissue unfortunately showed only skeletal muscle and some blood vessels. The amputation of the right leg was remarkable only for the ischemic degeneration of the muscle and a moderate arteriosclerosis. In summary, I think we can say that the gingival biopsies and the biopsies of the iliac bone marrow revealed a reticuloendothelial hyperplasia, the nature of which we cannot further specify.

DR. REINHARD: On reviewing this patient's record, I was impressed with the fact that the patient had an irregular fever, an elevated serum globulin and a significant increase in plasma cells, reticulum cells and monocytes in the bone marrow. Several years ago I reviewed the causes of increased numbers of plasma cells in the bone marrow, using our own cases in the hematology division as well as case reports in the literature. The diseases which were to be noted were the following: Hodgkin's disease, carcinoma of the liver and the biliary system, carcinoma of the stomach, any carcinoma with a leukemoid reaction, the granulomatous diseases, pulmonary or disseminated tuberculosis, fungus infections, syphilis, typhus, cirrhosis of the liver, obstructive jaundice and arsenic poisoning. Now let us try to eliminate as many of these as we can. This patient certainly did not have obstructive jaundice. Liver function tests showed some impairment. Do we have to consider the diagnosis of cirrhosis or do you think we may consider this to be a part of the generalized disease process? Dr. Recant, how about it? Do you think we have to worry about cirrhosis in this case?

DR. LILLIAN RECANT: I think the findings in this patient are compatible with cirrhosis of the liver and I don't know how one could rule that out. The bromsulphalein retention, the lowered serum albumin, the elevated serum globulin, the positive cephalin flocculation and the low serum cholesterol are certainly in keeping with a cirrhotic process in the liver.

DR. REINHARD: Do you think it would be fair to say that the patient had cirrhosis? Could this have accounted for the whole picture—peripheral neuritis? the mouth lesions?

DR. RECANT: Well, peripheral neuritis can be seen in cirrhosis. Certainly the mouth lesions would be extraordinary.

DR. REINHARD: Now let us consider the two major categories which I noted, namely malignant tumors and granulomatous infections. This patient did not have a leukemoid blood picture therefore we may perhaps concentrate our attention on certain tumors that are more apt to produce an increase in plasma cells in the bone marrow without generalized alteration of the blood and marrow cells. As I mentioned, carcinoma of the stomach has been observed to do this. The gastrointestinal x-rays showed no evidence of tumor although the stomach was not normal. Dr. Humphrey, what percentage of gastric carcinomas can be missed when a single examination is performed? This patient had two.

DR. HUMPHREY: Well, this depends on the individual examiner. It ranges all the way from zero up to perhaps 93 to 95 per cent.

DR. REINHARD: In 1938, a patient was seen at Barnes Hospital who died with metastatic cancer of the liver. At autopsy nothing was found in the stomach, but when the micro-sections of liver were studied, the tumor had the appearance of cancer, primary in the gastrointestinal tract. The prosector then reviewed the gross material and a tiny carcinoma of the stomach was found. The primary tumor was so small that it had been missed on the original examination of the stomach. Dr. Moore, do you think we have to worry about a primary tumor of the stomach in this patient?

DR. CARL MOORE: I think this is a diagnosis which still is a possibility. I saw the patient to whom you referred. He also had an increased number of cells in the peripheral blood and bone marrow which were thought to be either monocytes or reticulum cells. In retrospect when the answer became available, I rather imagine that these cells might well have been undifferentiated carcinoma cells. With regard to today's case, I went over the bone marrow sections again this morning and to the best of my knowledge, the reticulum cells and monocytes were straight reticulum cells and monocyes.

DR. REINHARD: The plasma cells were increased?

DR. MOORE: The plasma cells were definitely increased. I still believe the diagnosis of gastrointestinal tumor must be considered as an outside possibility but not a very likely one.

DR. REINHARD: Dr. Sherry, do we have to be concerned about a primary tumor of the liver?

DR. SOL SHERRY: Well, everybody seems to be hedging in this situation. We're going to end up with either a neoplastic or granulomatous disease. I suppose we have to give serious consideration to any type of neoplastic disease which could give this picture. Now certainly the hepatic function tests are not the ones that are usually seen with primary neoplastic disease of the liver. The alkaline phosphatase was entirely normal and it certainly would be unusual to see these neurologic lesions and oral lesions with carcinoma of the liver. I think this is an unlikely possibility.

DR. REINHARD: It seems to me that one would have to diagnose multiple diseases if this was one of the correct diagnoses. Now we come to Hodgkin's disease. This is more difficult to exclude. Hodgkin's disease can involve the meninges and produce bizarre neurologic findings. To my knowledge it rarely produces the neurologic picture seen in this patient. Dr. Harrington do you have any comments about the possibilities of malignant lymphoma in this patient?

DR. WILLIAM HARRINGTON: I think that it is possible but not likely.

DR. REINHARD: I would like to go over the neurologic findings briefly. These findings are summarized from a note by Dr. Charles Carter, the neurology resident. "There was some interosseous muscle atrophy. There were absent knee and ankle jerks bilaterally. There were calf fasciculations and an impairment of vibration and position sense in the feet. There was a bilateral foot drop and there was a question of a sensory and proprioceptive level, at about T eleven but this level was not convincing." Dr. Levy, what does this combination of findings suggest to you as the neurologic lesion?

DR. IRWIN LEVY: I think this suggests a peripheral neuropathy.

DR. REINHARD: Dr. Eisen, let us consider the patient's skin and mucous membrane lesions. Dr. Lane saw this patient but he was not able to come to the conference today. I would like to read his note which provides the best description of the lesions in the chart. "There is a granular, rough, ulcerated surface of the upper and lower gums extending on to the hard palate, the buccal surface of the cheek and the floor of the mouth. The ulcers are small and punched out for the most part and the entire area shows telangiectasis and dilated blood vessels. The dorsum and sides of the tongue are covered with a thick yellow-white adherent growth. The eruption is only slightly sensitive and feels better when dental plates are worn. This lesion appears granulom-

atous suggesting the old lesion seen in syphilis. Tuberculosis also gives a similar picture, but the ulcers are usually extremely tender. The minimum tenderness and pain also rule against an acute infection. A picture similar to the present may occur in the lymphoblastomata but the blood picture makes this unlikely." In addition to the mouth lesion, there were skin lesions. These were described on admission as petechiae in both flanks. Later these became confluent and there was an extensive confluent hemorrhagic eruption over both lateral aspects of the body. One observer described the skin of the head and neck as "golden bronze" in color and several observers described a lemon yellow tint to the skin of the body and extremities. One observer mentioned that there was several macules on the patient's back. Now Dr. Eisen, does this combination of bizarre findings ring any bells?

DR. HERMAN EISEN: No, there is a conspicuous absence of any sound in my head. With respect to this constellation of findings, I would suppose that the absence of a positive serologic test for syphilis would be strongly against this man having syphilitic disease of his mucous membranes and of his skin. As a matter of fact, there is a reference in the protocol to a solitary crusted lesion on the hypothenar eminence of the hand. Now one could also wonder whether or not this is a gumma. But, again I think the absence of a positive serologic test would make that extremely unlikely.

DR. REINHARD: What would be apt to happen to a gumma if you periodically peeled it off with your pocket knife? Apparently, the patient spent considerable time doing this.

DR. EISEN: I really don't know. I don't know what I'd call the lesion on his hand. I don't know whether this eruption you described on his flanks is an eruption or simply an extremely large ecchymosis. But in any case I can't offer any diagnostic possibilities. One thing which did occur to me in reading the protocol was that such a bizarre picture may be presented by primary amyloid disease which could even produce mouth lesions. I do think however, the several biopsies would exclude that possibility.

DR. REINHARD: Dr. Smith, several people thought of syphilis as being a likely diagnosis here. They mentioned that syphilis is one of the granulomatous lesions that can produce an increase in globulin and in plasma cells in the bone marrow and the mouth lesions were considered compatible with this diagnosis. How seriously do we have to consider this? The patient had three negative cardiolipin reactions and the spinal fluid Wassermann and colloidal gold tests were negative.

DR. JOHN SMITH: I certainly considered it somewhat originally. There is that history also of hip shots, the nature of which apparently aren't known. However, in the absence of a positive serologic test for syphilis or in the absence of any evidence of it in the spinal fluid, I think there is little to rest upon in the matter of syphilis.

DR. REINHARD: Before considering other granulomatous infections we should review the cultures which were obtained on this patient. Dr. Harford prepared this data for me. Culture of the oral secretions showed a heavy growth of Neisseria and of Alkaligenes and a moderate growth of an organism which was thought to be Hemophilus. Special cultures for fungus were negative. The biopsy specimen of the buccal mucous membrane was cultured for fungus and showed nothing but penicillium which was thought to be a contaminant. Bone marrow, spinal fluid and blood, cultured routinely and for fungus showed no growth. The urine grew out a Staph. albus. During the terminal part of the patient's illness, five blood cultures were done is which the findings were negative. These were cultured routinely as well as in special media, using the special procedures usual in subacute bacterial endocarditis. Dr. Harford, what infections do you think we can reasonably exclude on the basis of this data? Can we rule out any of those we have been talking about? What is the possibility for example that the lesion in the mouth could be a fungus infection? What is the possibility of the patient having a bacterial endocarditis?

DR. CARL HARFORD: I think it is possible to have a fungus infection in spite of the fact that the cultures were negative. I think this is similar to the problem of negative data in general. When they are negative there may be some extenuating circumstance which accounted for it. At the present time it is very difficult to rule out these things on the basis of negative evidence.

DR. REINHARD: Would you say that it is easier to miss an infection such as tuberculosis and fungus infection than to miss a bacterial infection?

DR. HARFORD: Yes, I think it is.

DR. REINHARD: Now considering the fungus infections, we remember that the patient had this

crusted ulcerative lesion on his hand for two years prior to his febrile terminal course. I thought a lot about this lesion and wondered what it might be. Of course it might be an epidermoid carcinoma. This would be expected to have become more prominent after a period of two years. Now, I believe, there are a good many fungus infections which may start with an ulcerating lesion on the hand. Dr. Rouse, I wonder if you could discuss some of the fungus infections that can start with ulcerating lesions on the extremities as the initial manifestation of the disease?

DR. ERNEST ROUSE: I thought that granulomatous disease was a real good possibility in this situation. I also believed that fungi should be considered very strongly. When one has a skin, mucous membrane or pulmonary lesion I think one of the things you must think of first is blastomycosis. I must say I was more impressed in the protocol with the pulmonary lesion than I was with the films as we saw them.

DR. REINHARD: I think it should be emphasized that the nodular lesions which were described on the initial roentgenogram subsequently diminished considerably and were therefore thought to be due to congestive failure.

DR. ROUSE: This lesion on the hand seems to me to be a cornified, hyperkeratotic lesion which was not suppurative. One would expect a blastomycotic lesion of this duration to suppurate and to spread through the lymphatics. We have no record of any lymphadenopathy. The lesions of the mucous membranes of the mouth could be consistent but I certainly would expect some neck lymphadenopathy in that situation. The lung lesions are not impressive. Actinomycosis is another fungus lesion which I think should be mentioned. It also would suppurate. It is a common invader of the mouth and because it spreads through connective tissue would almost certainly be a suppurative lesion in this duration of time with fistulas or sinuses established. Histoplasmosis is not very common as far as the skin is concerned. Of course it would fit in nicely with the mucous membrane lesions, the hepatomegaly, the evidence of fever and the disseminated disease process. Now there are fungi such as sporotrichosis which could begin on the periphery, the extremities and the exposed portions. Almost certainly during this time it would have spread by the lymphatics with appearance of other nodules up the arm. There are other lesions which can begin in this fashion such as geotrichosis. But that should be recognized in the mouth by having the same appearance as monilial thrush. I do not believe this represents a typical picture of any one of these fungus diseases. I think if you had to choose one, it would come closer to histoplasmosis than it would to the others.

DR. REINHARD: This was the diagnosis that was repeatedly considered while the patient was in the hospital—histoplasmosis. Now Dr. Rosenbaum, actinomycosis blastomycosis and coccidioidomycosis may all involve the spinal epidural space and the adjacent vertebral bodies producing a myelitis. Now are the neurologic findings in this case at all compatible with myelitis rather than peripheral neuritis or may we exclude that? There were no lesions in the vertebrae in the x-rays.

DR. HERBERT ROSENBAUM: I think you pretty well excluded anything that would be primarily a myelitis. Certainly the diseases mentioned can produce chronic infection and meningitis but the clinical picture here is most reminiscent of a peripheral neuropathy and we have no reason to suspect any infection directly involving the spinal cord or the cerebral spinal fluid.

DR. REINHARD: You will recall that we listed typhus as one of the causes of increased plasma cells in the bone marrow. This has been observed in many cases of typhus. I know of no reports of increased plasma cells in the bone marrow in other rickettsial diseases but from the nature of the lesion it seems probable that rickettsial diseases in general may produce such a response. Furthermore, several rickettsial diseases produce a hemorrhagic skin rash characterized by purpuric macules. Dr. Harrington you were asked to see this patient because of his purpura. Are you certain that this was a simple purpura and not a purpuric rash.

DR. HARRINGTON: Clinically I thought it was a purpura and the histology would be in favor of that also.

DR. REINHARD: Dr. Harford, are there any rickettsial infections that could account for this patient's major clinical and laboratory findings?

DR. HARFORD: I think not, Dr. Reinhard. I think the point you already asked Dr. Harrington about is a very important one, namely that in both typhus and in spotted fever, when one gets a hemorrhagic rash, it is always on the basis of a preceding maculopapular rash, and that apparently was not the case here. The distribution of this rash also is not consistent with

either typhus or spotted fever. With spotted fever there is usually an involvement of the extremities and of the face. With typhus fever, there is usually an involvement of the entire trunk. These features are not completely diagnostic but I think they are helpful. The fever also was somewhat intermittent as I read the protocol and then, as far as I can tell, the petechiae antedated the fever. Usually, in rickettsial infection, there is a prodromal period of fever before the rash breaks out; it usually begins as a maculopapular rash and when it becomes hemorrhagic does so a little while later. One other small point is that apparently this fever did not respond to tetracycline. If it were a rickettsial fever, it should.

DR. REINHARD: The patient may have had multiple unrelated disorders. However, let us assume for the moment that all the principal symptoms, physical signs and laboratory findings are due to a single disease process. By midnight last night I had worked down the list of disorders and believed that none of them would account for all the clinical manifestations. This left only arsenic poisoning as a possibility. At that time I was in a state of mild exhaustion and was quite ready to throw in the towel and assume that this case was completely beyond diagnosis. However, thinking about it further, I was impressed with the fact that the patient had anorexia, weight loss, weakness, fatigue and mucous membrane lesions resembling a granulomatous process but microscopically no granulomatus lesions were seen. There was a peripheral nephritis. There was a gastritis with very prominent rugae in the stomach. Hemorrhagic skin lesions were present. Hepatic dysfunction was noted. All these things are certainly things that can occur in arsenic poisoning. Dr. Eisen, from the description, do you think the mouth lesions in this patient are compatible with chronic heavy metal poisoning?

DR. EISEN: I don't really know but it is a possibility. I would say that in arsenic poisoning, hyperkeratosis on the palms is a conspicuous finding. In addition, usually the lesions are multiple and I gather this was a solitary lesion.

DR. REINHARD: And it was on the dorsum of the palm?

DR. EISEN: No, it was in the right place. Was it not on the hypothenar eminence? It was on the right surface for arsenic lesions but it was a solitary lesion and that would be against it.

DR. REINHARD: Dr. Recant, you're an expert on arsenic poisoning, what do you think about this diagnosis? I was intrigued to discover that hemorrhagic skin lesions occur in chronic arsenic poisoning. How about the mucous membrane lesion? I wasn't able to find much on that. Do you know anything about it?

DR. RECANT: Apparently mucous membrane lesions may occur but these usually occur with the oral ingestion of arsenic. From the small experience I have with this subject mouth lesions do not appear to be a prominent aspect of arsenic intoxication. Certainly the skin lesions with the hemorrhagic tendency are consistent and in fact arsenic is defined as a vascular-type poison affecting the smaller blood vessels.

DR. REINHARD: Are you intrigued by the possibility of heavy metal poisoning here or does this seem very far fetched?

DR. RECANT: Well, if you need some support I am somewhat intrigued by this. Certainly the possibility of chronic arsenic intoxication could explain a large number of the observations made. I might just point out one thing about the liver lesions with arsenic intoxication. It is usually the inorganic arsenic, Fowler's solution, that is most commonly associated with the benign cirrhotic processes. Most of the other arsenics are associated with acute or subacute processes more like the yellow atrophies. This patient presumably received organic arsenics, if any, and hence does not seem to fit into either of the two categories.

DR. REINHARD: Now how about bismuth or mercury poisoning? Does not one get a somewhat similar picture with peripheral neuritis?

DR. RECANT: Yes.

DR. REINHARD: I would like to discuss this further but I am afraid the time is up and I am sure we are not going to be able to arrive at a final diagnosis. I would like to present as my final diagnosis in this case, heavy metal poisoning. This would account for all the findings in this case except the anterior rectal mass which might have been a tumor. Dr. Edwards will now present the autopsy findings.

PATHOLOGIC FINDINGS

DR. EDWARDS: The body was that of an elderly white man who was well developed and moderately well nourished. There was a slight yellow tint to the unexposed skin; the exposed skin had a brown coloration. The right lower extremity had been amputated at the mid-thigh level and some purulent drainage from the partially healed stump incision persisted. The right femoral artery beneath the embolectomy

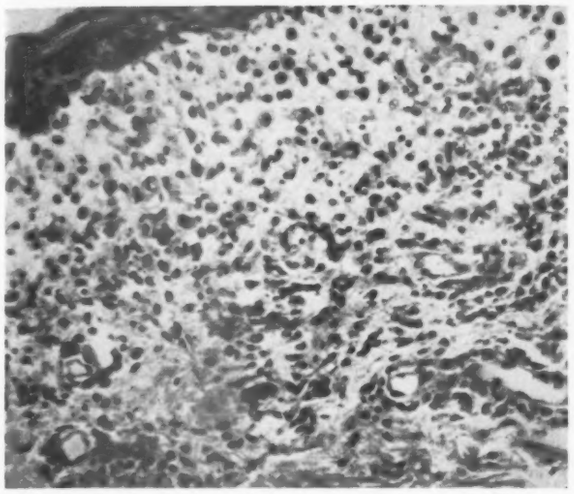


FIG. 1. Photomicrograph of the skin. There is a nodule of histiocytes and leukocytes in the dermis.

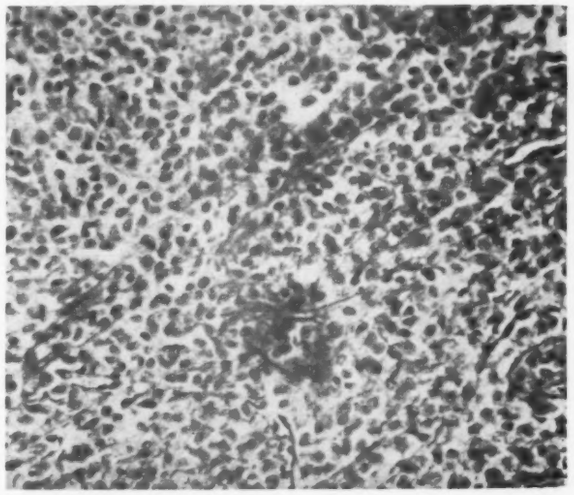


FIG. 2. Photomicrograph of the tongue. A dense infiltration of histiocytes is seen in the submucosa.

incision contained an adherent thrombus and the artery itself was quite sclerotic. There was a petechial rash of the flanks and back and a section through this area (Fig. 1) disclosed a nodule of histiocytes. It was a fairly small nodule; there were a number of these large pink cells with abundant cytoplasm and, in addition, some lymphocytes and a few plasma cells, as well as a number of capillaries proliferating in this lesion.

In the mouth there were several 2 to 3 mm. raised gray-red lesions on the sides and dorsum of the tongue and on the alveolar ridges. Some of these were ulcerated and the tongue in general had a somewhat thick coat. These lesions (Fig. 2) showed a dense infiltration of histiocytes with abundant cytoplasm and, in addition, a more sparse infiltrate of smaller cells—plasma cells and lymphocytes. There was some fibrosis of a slight degree as well as a proliferation of capillaries giving a very faint suggestion of granulation tissue. The overlying epithelium was slightly atrophic. This closely resembled the section received at biopsy. Upon opening the thorax, there was 250 cc. of serous fluid in each of the three serous cavities. The lungs were heavy. They weighed 1,400 gm. and were firm. There were some patchy atelectasis posteriorly and emphysema at the margins and on cut section they were moist and red. Radiating out from the hilar areas (Fig. 3) there were fine bands of fibrous tissue

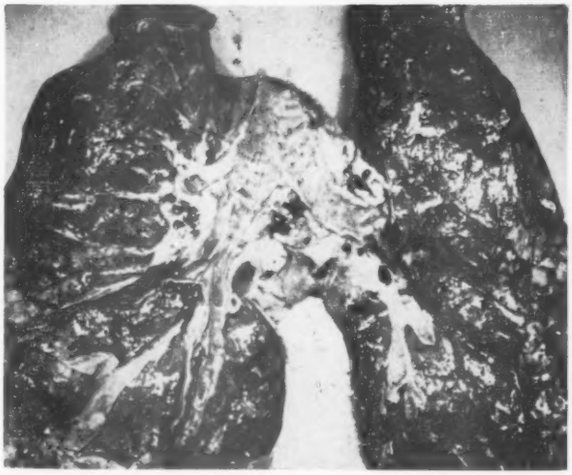


FIG. 3. Gross picture of the lungs showing the white fibrous accentuation of the interlobular septal markings in the perihilar areas.

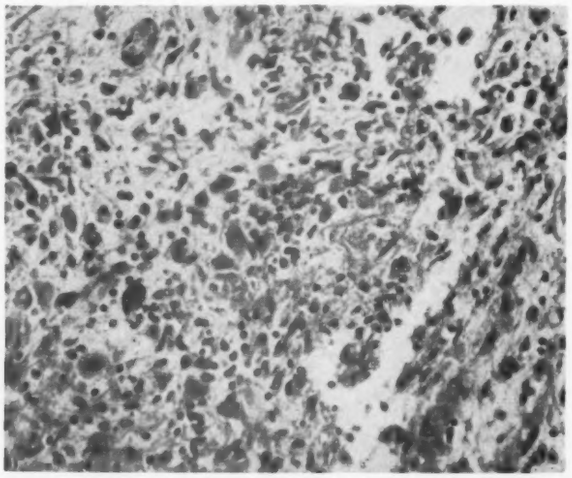


FIG. 4. Photomicrograph of the lung. Loose fibrous tissue growing in the interstitial substance is accompanied by an infiltration of large histiocytes and smaller lymphocytes.

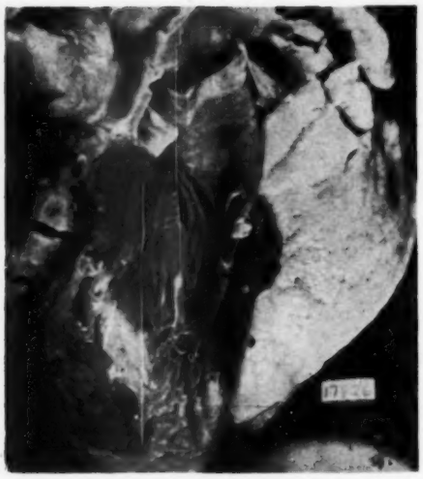


FIG. 5. Gross picture of the heart portraying the confluent raised epicardial thickening.

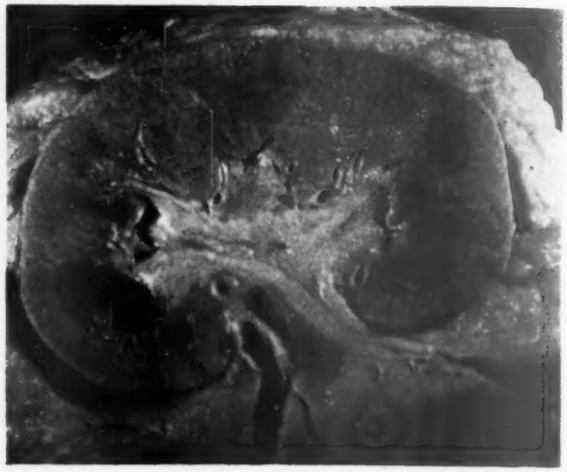


FIG. 6. Photomicrograph of the heart. Fibrous tissue and histiocytes invade the epicardial fat from the epicardial surface. A small bundle of myocardial cells is in the lower left.

which were most prominent in the upper and middle lobes. These seemed to accentuate the architectural markings. These fibrous bands (Fig. 4) microscopically were composed of loose hypocellular fibrous tissue which was located in the interstitial spaces, not actually within the alveoli, and did not represent an organizing pneumonitis. The fibrous tissue was infiltrated by a variable number of these histiocytes with abundant pink cytoplasm. There were other more cellular areas with the other inflammatory cells, including lymphocytes and plasma cells along with the abundant fibrous tissue histiocytes and slight vascularization.

The heart weighed 370 gm. and the coronary arteries were markedly sclerotic. There was an old calcific occlusion of the left anterior descending branch. Near the apex there was a well healed old fibrotic infarct of the anteroseptal area in which the wall was almost completely replaced by fibrous tissue. A high posterior septal subendocardial infarct was also present. The epicardium was thickened and opaque. (Fig. 5.) Multiple confluent slightly raised gray-white smooth areas gave a pearly appearance to the epicardium and extended over all the places in which one normally finds epicardial fat. The microsection of one such area (Fig. 6) showed the epicardium to be infiltrated by a large amount of fibrous tissue immediately beneath the visceral pericardium. In this fibrous tissue there were similar histiocytes and a scattering of lymphocytes and plasma cells. The fibrous tissue infiltrated down into adjacent fatty tissue, between lobules of fat and between individual fat cells. Again there were varying proportions of histiocytes and inflammatory cells and fibrous tissue. The fat cells between the infiltrate were atrophic and not frankly necrotic. The evisceration of the abdominal cavity was made extremely difficult due to the character of the retroperitoneal fat. It was very firm by reason of the presence of fibrous bands coursing through the fat and one could not dissect it bluntly with the fingers.

The kidneys (Fig. 7) were completely encapsulated in a broad capsule of fatty tissue; there were many firm linear bands of white fibrous tissue coursing throughout the fatty tissue. The peripelvic fat of the kidneys was a mottled brown-yellow, was very firm and blunted the collecting system a little. Microscopically, fat had been completely replaced by proliferation of fibrous tissue and dense infiltration of histiocytes and other inflammatory cells. The renal pelvic lesions were more cellular than most of the lesions described. There was a slight bit of necrosis within the tissue, but no acute fat necrosis. The adrenals were similarly encased in this fat and microscopically (Fig. 8) there were broad bands of fibrous tissue breaking up the fat lobules. Again the character of the infiltrate, focal hemorrhage and atrophy and destruction of fat without acute necrosis was similar to the process elsewhere. None of these macrophages were foamy or fat filled and, with special fat stains, very little fat was demonstrated in any of the histiocytes. The perirectal and the retroperitoneal fat and all the perivisceral fat except the

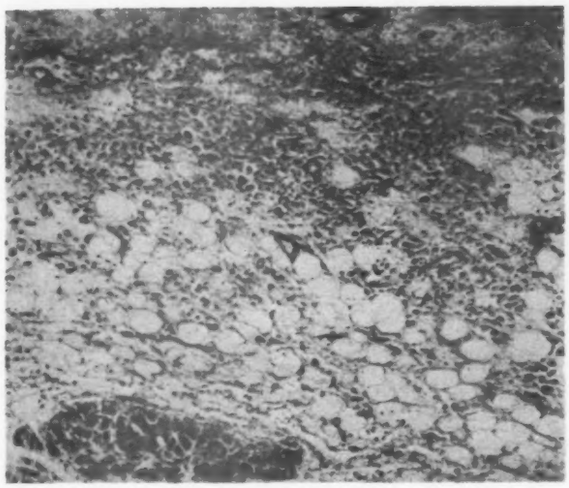


FIG. 7. Gross photograph of the kidney showing the encasement of the kidney in the firm capsule of altered fat and the mottling of the peripelvic fat.

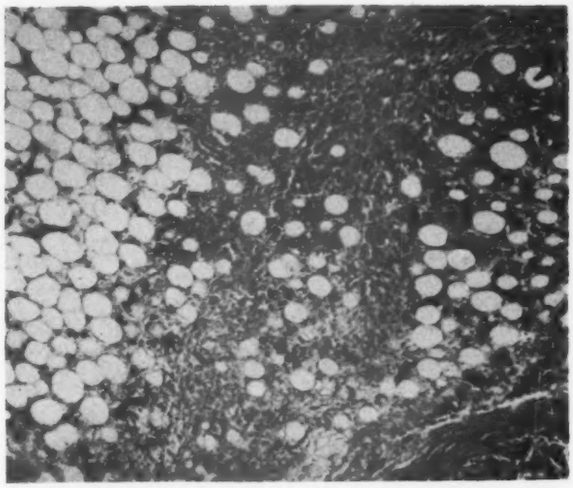


FIG. 8. Photomicrograph of the adrenal gland and adjacent fat. Fatty tissue is invaded by fibrous tissue and large histiocytes. Adrenal cortex is in the lower right.

mesenteric and omental fat was similarly involved. The mass that was felt clinically in the rectum was most probably a nodule of this fatty induration.

The lymph nodes throughout the body were remarkable due to their small size. There were very few of them found. Grossly they appeared normal but microscopically there was a generalized depletion of the lymphoid elements in the node. In the peripheral sinusoids there was prominence of the reticular cells without any lymphocytes and the lymphoid tissue generally was depleted. There were nodular infiltrates of histiocytes with necrosis in the center of the nodules. The liver weighed 1,400 gm. and was soft. The architectural markings were prominent with confluent red central areas grossly. Microscopically (Fig. 9) there was a moderate central congestion and diffusely, throughout the liver, there was infiltration of the sinusoids mostly by lymphocytes, some plasma cells and a few neutrophils and eosinophils which occasionally formed big collections, but most of it was diffuse infiltration. In addition there was some focal necrosis within the liver. The spleen was very large, soft, red and mushy and bulged on cut

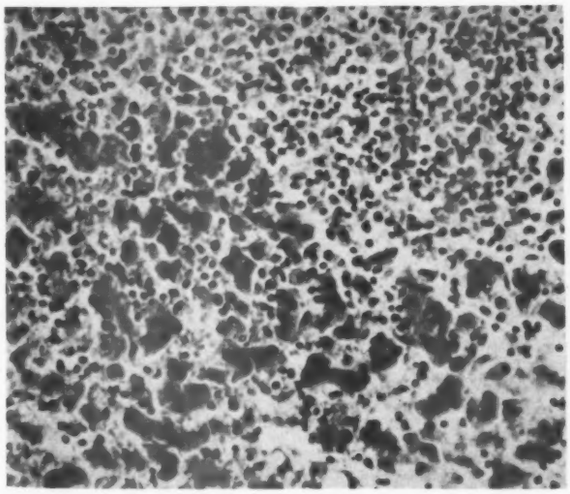


FIG. 9. Photomicrograph of the liver. There is a small nodular infiltration of inflammatory cells. The sinusoids are congested and they contain a more diffuse infiltration by inflammatory cells.

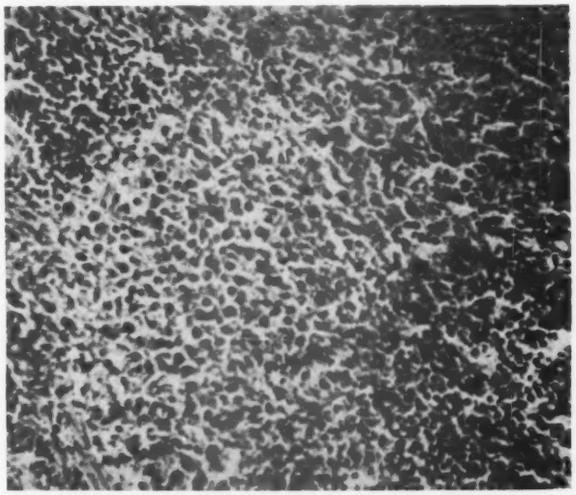


FIG. 10. Photomicrograph of the spleen. There is a nodular aggregation of histiocytes with necrosis of one portion of the nodule.

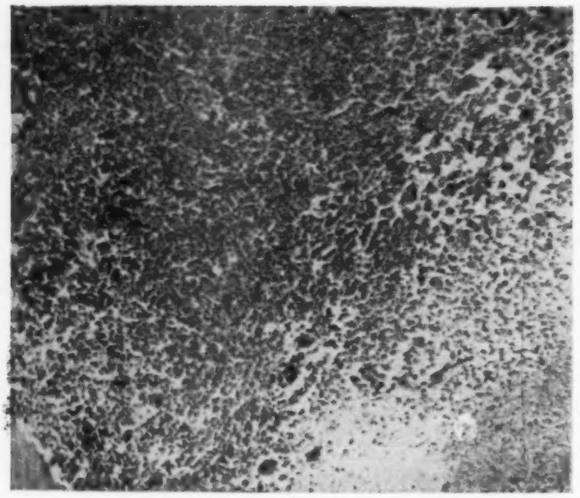
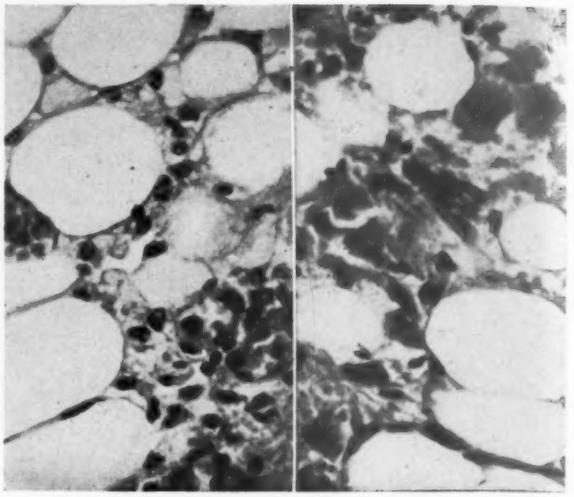


FIG. 11. Photomicrograph of an osteolytic lesion of a vertebra. There is a large area of necrosis in the lower right which is surrounded by an infiltration of histiocytes.



A B

FIG. 12. Left side of the photograph shows subcutaneous tissue of the right thigh. Fat necrosis with degenerating fat cells, foamy fat-filled macrophages, hyperemic capillaries and inflammatory cells. Right side shows periadrenal fat. Histiocytes with large solid eosinophilic cytoplasm are accompanied by fibroblasts and some lymphocytes and atrophy of fat cells without phagocytosis of fat.

surface. It had the typical gross appearance of acute splenic hyperplasia with several small yellow infarcts. Microscopically (Fig. 10) there were many nodules of histiocytes present in the spleen; focally there was complete loss of nuclear staining representing necrosis within these nodules. The splenic pulp had an increased number of histiocytes and some neutrophils diffusely.

In the lumbar vertebrae there were several 5 mm. to 1 cm. osteolytic yellow lesions which involved both the cancellous and cortical bone. A microsection of one such lesion (Fig. 11) showed complete necrosis of marrow cells and complete loss of the bony elements. This area was surrounded by a broad band of large cells, many histiocytes with a couple of giant cells here and there and, surrounding this zone, some lymphocytes, plasma cells and other cells of infiltrate. There were some fragments of destroyed bony spicules at the edge of the lesion. At a higher magnification some of the giant cells had some phagocytized cells within them. A section at a low power of the cortical bone showed that it was interrupted in one place by this destructive process which streamed out through this defect in the cortex to lie out in the perivertebral fatty tissue where it resembled the fatty lesions described before. There was a 1 cm. retroperitoneal abscess near the spleen and in this lesion there were some gram positive cocci. The blood culture also grew out Staphylococcus aureus. Cultures of other tissues including tongue, lung, epicardium and adrenal were contaminated at the time of taking and grew out a motley assortment of contaminants.

In the gastrointestinal tract there was a 7 mm. ulcer in the pylorus. There were focal erosions of the esophagus and in the rectum there was a stalk of the polyp which had been biopsied. A microsection of the subcutaneous tissue around the amputation site (Fig. 12A) showed the picture of fat necrosis that is in contrast (Fig. 12B) with that which was seen in the fatty tissue elsewhere. There were large foamy cells that were filled with abundant fatty material and more of the acute infiltration of lymphocytes and a few neutrophils. The hyperemia and vascularity of the lesion was quite different from the changes described before. This lesion represented then, traumatic fat necrosis in the resolving stage. Special stains on the perivisceral fat for fungi and acid fast bacilli and other bacteria were negative with the exception of the cocci seen in the retroperitoneal abscess. The Oil-red-O stain for fat showed no fat in most of the histiocytes and a minimum of fat in a very few of them.

DR. THOMAS: As Dr. Edwards had demonstrated, this eighty-two year old man had an impressive array of lesions in almost every type of tissue in the body. In general these lesions

were characterized by fibrosis, an inflammatory cell infiltrate consisting principally of histiocytes and by occasional foci of necrosis. My role in the proceedings today is to try to put all these various observations together and at least from the anatomic standpoint, fit them into some familiar entity. I do not mind telling you that this has proved to be an exceedingly difficult task. Dr. Edwards took at least a hundred sections for microscopic study and many of us in the pathology department have examined them.

None of us can recall seeing anything similar in an elderly person and we have been unable to find anything similar in our autopsy index which includes 17,000 autopsies.

At the time of the gross autopsy, with the observation of the extensive involvement of the fat, our thoughts turned to Weber-Christian's disease. However, the histologic picture is certainly not that of Weber-Christian's disease. In that disease there is extensive fat necrosis with an acute inflammatory reaction which is not what we found here. Another thing that occurred to us was lymphoma but the histologic picture is not that of a lymphoma. The lymphomas that we are familiar with are not characterized by the type of infiltrate that we have here. We also considered infectious processes of one sort or another. Dr. Edwards took numerous types of material for cultures at the time of autopsy but none of these helped us in making a diagnosis.

We attempted to stain organisms in the tissue but have not succeeded in demonstrating any except in an abscess which contained staphylococci. This abscess is probably a terminal process and not related to the underlying disease. As Dr. Harford pointed out, negative findings do not necessarily rule out a bacterial or a fungal disease but certainly with the amount of material we examined at autopsy, it is unlikely that we would have missed any of the common bacterial or fungal organisms. There are certain features that bring to mind viral infection; Dr. W. S. Hartroft tells me that if he were given the liver alone, he thinks he would classify it as an atypical viral hepatitis. But when we consider all the manifestations in this patient we cannot diagnose any type of viral disease with which we are familiar.

I seem to be eliminating practically everything. What does this man have? Actually I do not know but the conditions that his disease most resembled in my mind are the histiocytic diseases that we see in children, such as Letterer-Siwe's and Schüller-Christian's disease. However, the histologic picture is not really typical of any of these conditions, although it does resemble the conditions we call histiocytosis more than anything else. However, I must emphasize that with the evidence at hand, we can not really classify this man's disease into any known category. It may well be that what we have had demonstrated here is an entirely new entity.

ADDENDUM

A recent case report by Goldner and Volk (*Arch. Int. Med.*, 95: 689–698, 1955) has been called to our attention. The disease reported by these authors in a sixty-seven year old woman resembles that in our patient in many respects and a diagnosis of histiocytosis was made.

Case Report

Some Observations on the Effect of Heart Rate Controlled by an External Stimulator in Aortic Insufficiency*

MORTON LEE PEARCE, M.D. *and* ROBERT NORDYKE, M.D.
Los Angeles, California

PROLONGED periods of ventricular asystole in a forty-eight year old man with "free" aortic insufficiency and complete A-V block required the constant use of an external electrical pacemaker [*1*] for over two weeks. A detailed account of the clinical aspects of the case is presented elsewhere [*2*] and only a brief recapitulation will be given here (see addendum). The complete control of heart rate afforded by the pacemaker permitted a series of observations on the effect of heart rate in aortic insufficiency.

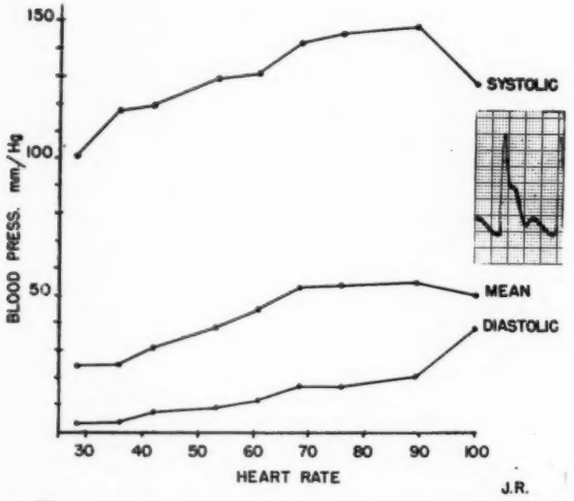


FIG. 1. Systolic, diastolic and mean blood pressures plotted as a function of cardiac rate. A single pressure pulse recorded when the heart rate was 90 per minute is displayed to the right.

When aortic insufficiency is produced experimentally, tachycardia usually occurs [*3*]. Clinically, patients with aortic insufficiency often have tachycardia, particularly after effort or in the presence of heart failure. This is in contrast to the relative bradycardia seen in aortic stenosis. It is probable that both of these responses have, within limits, a certain adaptive value.

METHODS

Regular ventricular contractions were produced by an external electrical stimulation [*1*]. The observations on arterial pressure presented in Figure 1 were made by puncturing the left brachial artery with a thin walled 18 gage indwelling needle. The needle was connected by lead tubing to a Sanborn electromanometer and recording was made on a direct writing oscillograph (Sanborn). The electromanometer was calibrated before and after the measurements. Mean blood pressure was obtained by electronic integration over several pulse cycles. The systolic and diastolic pressures also represent the average of several pulse cycles. The zero point is the level of the left auricle.

Venous pressures were measured with a saline manometer through the only available arm vein. This had already been catheterized with a fine polyethylene tube. There was a poor response of this system to maneuvers which should have produced a free rise and fall. These data are thought to be unreliable and are not presented.

The renal studies were performed with an indwelling catheter. Each collection period was terminated by washing out the bladder with distilled water and air. Endogenous creatinine clearance was used as a measure of glomerular filtration. Creatinine in serum and urine was determined by the method of Peters [*4*]. Clearance of para-aminohippurate was performed as outlined by Goldring and Chasis [*5*]. Sodium and po-

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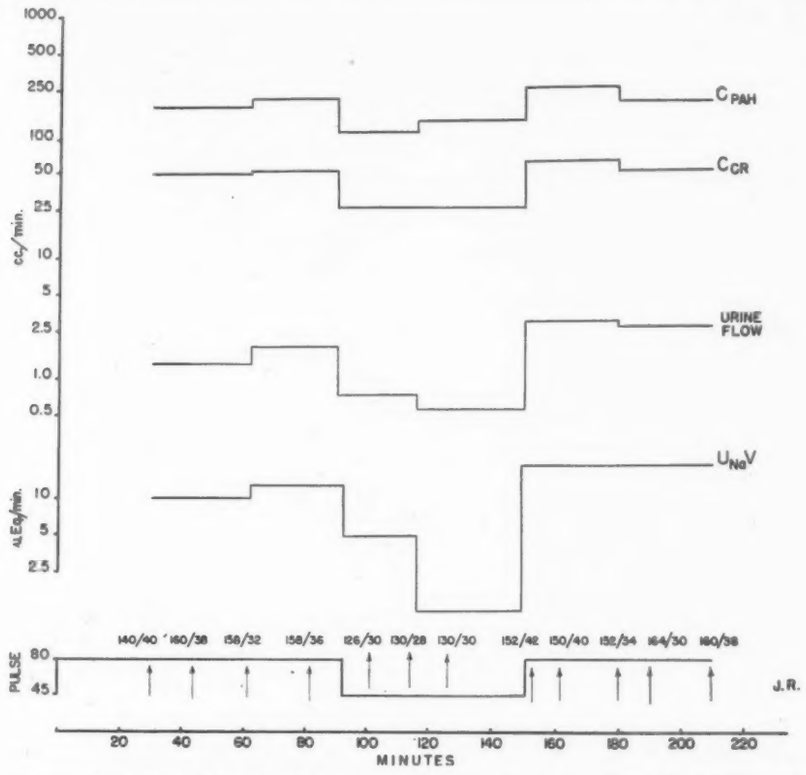

FIG. 2. The effect of slowing the heart rate on renal hemodynamics. Blood pressure observations were made by cuff.

tassium were measured with a Baird flame photometer employing an internal standard [*6*]. A potentiometer was employed for the chloride determinations [*7*].

The experiments were all performed with the patient in a semi-reclining position. The observations on arterial pressure were made on the fifth day on the pacemaker and the observations on renal function were made on the seventh and ninth days. His daily sodium intake was minimal for most of the period during the hospitalization except on the second day on the pacemaker when an attempt to produce spontaneous ventricular contractions with sodium lactate was made.

RESULTS

The first experiment was performed to determine whether the patient's heart responded in an "all or nothing" fashion to the pacemaker. Blood pressure was recorded directly from the left brachial artery. The cardiac pacemaker was set at a rate of 82 per minute. As the voltage of the stimulator was gradually diminished, no change was noted in the pressure pulses until a voltage was reached in which no response at all was obtained.

The results of the second experiment are charted in Figure 1. The single pressure pulse displayed was recorded when the cardiac rate was 90 per minute and the patient's condition appeared optimal. The rapid early systolic rise and late systolic collapse are typical of "free" aortic insufficiency. The pacemaker was maintained at each rate for one minute before arterial pressure was recorded. It can be seen that as the pacemaker was progressively slowed the pulse pressure failed to widen correspondingly. When the rate reached 68 per minute the mean blood pressure began to fall. The diastolic pressures recorded at the slower rates are commonplace for pressures recorded by sphygmomanometry in patients with aortic insufficiency, but they are remarkably low for pressures recorded by direct methods.

In the third experiment venous pressure was determined as the heart rate was slowed. The venous pressure was noted to fall progressively. However, the results of this experiment are not dependable since the only employable vein had been catheterized with a fine polyethylene tube and the pressures were measured through this.

In the experiment shown in Figure 2, renal plasma flow, glomerular filtration, urine flow and electrolyte excretion were determined at

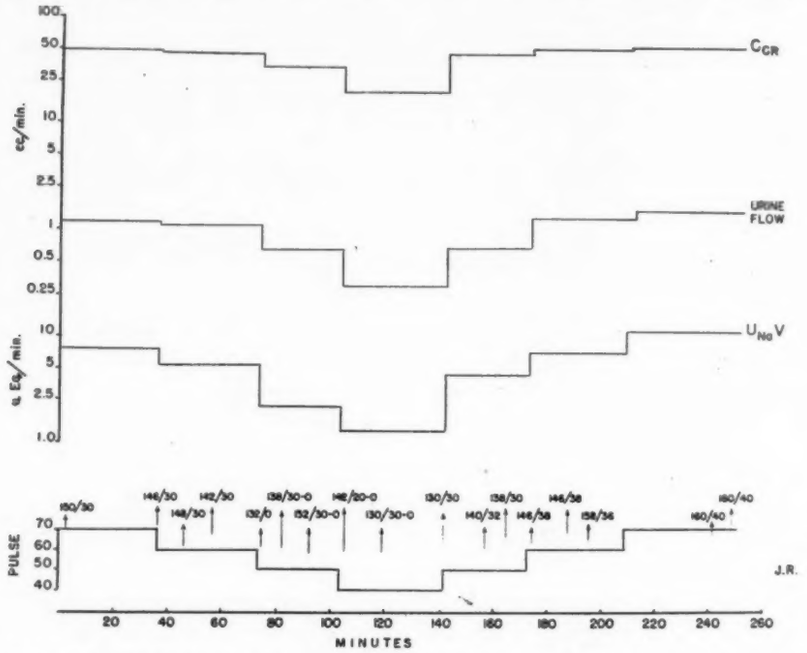

FIG. 3. The effect of stepwise slowing of the heart rate on glomerular filtration and urine and sodium excretion. Cuff pressures are recorded.

two different heart rates. The sodium excretion was not corrected for PAH excretion because at such low rates of sodium excretion most of the PAH was probably excreted in the form of potassium para-aminohippurate. By use of semilogarithmic charting it can be seen that as the heart rate is slowed, the percentagewise change in renal plasma flow and glomerular filtration is about the same. Urine flow and sodium excretion are affected in a more pronounced fashion. Potassium and chloride excretion diminished as the heart rate fell, but not as markedly as sodium. Chloride was intermediate between sodium and potassium. The serum values during this experiment were: Na 139, K 5.8 and Cl 95 mEq./L.

A second experiment on the effect of heart rate on renal function is shown in Figure 3. In this experiment PAH was not infused, but a more detailed set of observations was made as the pacemaker was first diminished ten stimuli per minute for half-hour periods and then similarly increased stepwise. The stepwise decline and rise in glomerular filtration rate and salt and water excretion is apparent. Again sodium excretion appeared to be the most sensitive indicator of the status of renal function as the heart rate slowed and increased and, presumably, cardiac output fell and rose. Potassium was the least sensitive with chloride in an intermediate position. Serum values during this experiment were Na 142, K 5.0 and Cl 98 mEq./L.

COMMENTS

Where the only variable was strength of stimulus, the response of the heart was "all or nothing." This is not surprising for the first demonstration of all or nothing was made employing the isolated heart and strength of stimulus was the only variable [*8*].

As discussed in some detail by Wiggers [*9*], the estimation of stroke volume from the pulse pressure is hazardous. It is thought that directional changes can be deduced from the experiment presented in Figure 1, since the only variable which was introduced was cardiac rate.

In the steady state in the normal subject cardiac slowing would, within limits, result in the following course of events: an increase in diastolic filling with a subsequent increase in systolic discharge, an increase in pulse pressure and, unless peripheral resistance is altered, no change in mean blood pressure.

The patient presented in this study followed the above sequence only as the heart rate diminished from 100 to 90 per minute. Below 90, however, decreasing the heart rate does not result in further widening of pulse pressure.

This may be due to a restraining action ("tamponade") of the pericardium to an increase in

diastolic filling in an already dilated heart. It is more likely that the left ventricle is no longer able to respond with a force proportionate to diastolic stretch and so at a heart rate below 90 per minute stroke volume falls rather than rises with diminishing rate. A normal myocardium might have responded differently, but we are dealing with a heart already in failure, and to increasing diastolic filling via the left auricle is added an increasing diastolic run-off from the aorta.

As the heart rate is reduced from 90 to 68 the mean blood pressure is sustained, suggesting that there is a compensatory peripheral vasoconstriction. However, even this mean blood pressure is in the range of clinical shock and is one which is maintained at some cost to renal blood flow. Below a pulse rate of 68, mean blood pressure falls along with the pulse pressure suggesting that the cardiac output has fallen to the level where even extreme vasoconstriction (shown in part by a fall of effective renal plasma flow from 200 to 125 cc. per minute) no longer maintains mean blood pressure and, presumably, the perfusion of vital areas such as the myocardium and brain.

If the venous pressures are meaningful, they suggest that the fall in stroke volume and mean blood pressure is due to increasing left ventricular failure rather than pericardial restriction. The latter would be expected to result in a redistribution of blood to the peripheral venous pool and a rising venous pressure. The fall in venous pressure with decrease in heart rate suggests that the blood redistribution was away from the periphery and toward the lungs and the heart itself.

Even at a heart rate which seemed optimal clinically, there is a considerable depression of renal plasma flow and glomerular filtration. These are undoubtedly due to the general clinical status of the patient. The fact that even at an optimal heart rate the mean arterial blood pressure was only 50 mm. Hg also contributed to the low values. The studies of Shipley and Study [*10*] show a progressive decline in renal plasma flow and glomerular filtration as mean arterial blood pressure is lowered below 80 mm. Hg. Except as an indication of diminished cardiac output, the fall in pulse pressure itself is probably not deleterious to the kidneys. Goodyer and Glenn [*11*] have shown that as long as mean blood pressure and blood flow are maintained, decrease in renal arterial pulsation has no effect on excretion of water and electrolytes, or on clearances of inulin and para-aminohippurate. In studies with a rotameter, Ritter has drawn similar conclusions regarding the effect of arterial pulsations on renal blood flow [*12*].

It would be difficult to assign the changes in water and sodium excretion noted here to a fall in glomerular filtration alone. In the experiment shown in Figure 2, the fall in renal plasma flow and glomerular filtration is about the same percentagewise while the fall in sodium excretion is considerably greater. This has been previously noted [*13*]. Whether or not sodium excretion can decline without any fall in glomerular filtration is uncertain, but the decline in sodium excretion is a very sensitive indicator of slight changes in renal hemodynamics. Certainly "glomerulotubular imbalance" alone does not explain the course of events [*13*], unless it is agreed that small reductions in filtered sodium result in increases of tubular reabsorption which in turn cause large reductions in the rate of excretion of urine sodium.

The very low values of sodium excretion obtained even at the higher heart rates is obviously a result both of the low renal perfusion pressure combined with a prolonged reduction in sodium intake.

Without aortic insufficiency, the deterioration of mean blood pressure and renal function with slowing of heart rate seen in this patient could be expected only at much lower rates. Aas and Blegen [*14*] have noted the usual patient with complete heart block maintains compensation at rates much lower than those which resulted in trouble for the patient in this study. A prolonged period of diastolic run-off as occurred here at the slower heart rates was apparently not compensated by increased systolic ejection. Vasoconstriction guarded the mean blood pressure down to cardiac rates of 68, but already at the expense of renal hemodynamics and salt excretion.

In the data of Kotte et al. [*15*] it is interesting to note that their diastolic values for direct arterial pressures in ten patients with aortic insufficiency were considerably higher than most of the values displayed here. As bradycardia became pronounced the diastolic pressure came close to zero in our study.

SUMMARY

The necessity of maintaining a patient with "free" aortic regurgitation on an electrical

pacemaker for several days permitted some observations of the effect of heart rate in this disorder. At rates below 90 per minute, stroke volume apparently did not maintain minute cardiac output. Peripheral vasoconstriction maintained mean blood pressure until the heart rate reached 68 beats per minute. Below this level, pulse pressure and mean blood pressure declined steadily. Even at higher heart rates, renal function as measured by renal plasma flow, glomerular filtration and urine and electrolyte excretion were very sensitive indicators of the decline of blood flow as the heart rate was reduced in small decrements. It is concluded that a relatively rapid heart rate can be advantageous in aortic insufficiency with heart failure.

Acknowledgments: Mr. Joseph Yamashita performed the electrolyte determinations.

ADDENDUM

The patient, a forty-eight year old actively employed Negro laborer, was admitted to Wadsworth General Hospital with a complaint of brief syncope followed by severe dyspnea several hours prior to entry. He had had known valvular heart disease for one and one-half years when study at another hospital revealed aortic insufficiency with congestive heart failure. At that time blood and spinal fluid tests for syphilis were negative. There was a past history of syphilis treated in 1930 and 1954, the latter time with 9 million units of procaine-penicillin.

Physical examination revealed a severely dyspneic and orthopneic Negro man. He was afebrile. The blood pressure was 140/30 in both arms. The pulse was 40 per minute and regular. The jugular veins were distended to the jaw. Moist rales were heard at both lung bases. The cardiac apex impulse was in the sixth intercostal space at the anterior axillary line. The second aortic sound was inaudible and there was a loud, rough, to-and-fro murmur heard best at the third intercostal space, left sternal border, but well transmitted over the entire precordium and into the neck vessels. No abdominal organs were palpable, and there was no peripheral edema. There were no skin or nervous system stigmata of syphilis.

Laboratory tests including serologic tests for syphilis were essentially negative. X-ray of the chest and fluoroscopic examination revealed marked left ventricular enlargement with a prominent and vigorously pulsating aortic arch. Complete heart block and left ventricular hypertrophy were seen on the electrocardiogram.

For about five weeks the patient had first degree A-V block with only one additional Adams-Stokes attack. However, thereafter he had complete heart block followed by frequent bouts of ventricular arrest, unresponsive to sublingual and intramuscular isoproterenol, ephedrine and atropine. The first day epinephrine prevented ventricular arrest but after that no medication was effective. An electrical pacemaker [*1*], previously used intermittently, was operated constantly. Sixteen days later, with the external pacemaker in constant operation, a Hufnagel valve was inserted without difficulty.* Postoperatively, spontaneous idioventricular rhythm ensued at a rate of 70. The patient died on the third postoperative day when a sudden ventricular asystole failed to respond to electrical stimulation.

At autopsy, aneurysms of the left and right aortic sinuses were found with thickening and depression of part of the left and right valve cusps. The left ventricle was markedly dilated and hypertrophied. The aneurysms were probably but not certainly of syphilitic etiology.

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Chronic Lymphocytic Leukemia Associated with Dysproteinemia and Acquired Hemolytic Anemia*

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QUANTITATIVE and qualitative alterations of plasma proteins have been previously reported in malignant lymphomas, including chronic lymphocytic leukemia [*1,2*]. In some instances these alterations were associated with the presence of immune antibodies, as a rule autoantibodies, against red cells.

The present report concerns a case of chronic lymphocytic leukemia associated with acquired hemolytic anemia and hemorrhagic manifestations, in which the abnormalities of plasma proteins were particularly striking.

CASE REPORT

The patient was a seventy year old white man with a history of progressive weakness, exertional dyspnea, generalized itching and bleeding tendency of six months' duration. During a previous hospitalization approximately four months before, no conclusive diagnosis could be made except for a normochromic anemia of undetermined origin. In spite of treatment with vitamin B_{12}, liver extracts, iron and blood transfusions, the condition did not improve. Congestive failure manifested by edema of the ankles, cough and oliguria was adequately controlled by digitalis. He had a history of hemorrhages from the gums, occasional epistaxis, petechial rashes and easy bruising.

The patient was a pale, poorly nourished white man. Skin abrasions, due to scratching, and petechiae were seen all over the body. Small, firm, painless lymph nodes ranging from 1 to 2 cm. in diameter were palpable in the neck, axillary and inguinal regions, on both sides. The heart was moderately enlarged to the left and there was a systolic murmur at the apex and at the base. The blood pressure was within normal limits. Diminished vocal fremitus, dullness on percussion and diminished breath sounds at the right base suggested the presence of a pleural effusion. The liver edge was three fingerbreadths below the right costal margin; the liver was smooth and firm. The spleen was not palpable. There was slight pitting edema of the ankles. X-ray of the chest revealed slight enlargement of the heart, right pleural effusion and a questionable enlarged lymph node at the right hilum. Electrocardiogram showed abnormalities consistent with mild coronary insufficiency.

Laboratory examination revealed the following: red blood cells 2,760,000 per cu. mm., hemoglobin 8.05 gm. per cent, mean corpuscular volume 84 cu. microns, mean corpuscular hemoglobin 29 gamma gamma, mean corpuscular hemoglobin concentration 35 per cent, reticulocytes 2.5 per cent, white blood cells 7,300 per cu. mm. The differential count showed 1 per cent stab cells, 46 per cent segmented granulocytes, 5 per cent eosinophilic granulocytes, 1 per cent basophilic granulocytes, 34 per cent lymphocytes, 13 per cent monocytes; platelet count 294,000; clot retraction normal; bleeding time 9 minutes, clotting time (Lee and White) eleven minutes; tourniquet test positive; prothrombin time (Quick) sixteen seconds (normal control thirteen seconds); prothrombin consumption test and antithrombin activity normal; osmotic and mechanical fragilities of red cells within normal limits. Over a period of four days, fecal urobilinogen averaged 10 mg. daily. The serum total proteins, as determined with the biuret technic, were 13.6 gm. per 100 ml. Paper electrophoresis (Spinco electrophoresis apparatus) revealed the following distribution of the fractions, expressed in gm. per 100 ml.: albumin 3.8, alpha globulin 1.6, beta globulin 0.6, gamma globulin 7.6. Tests for cryoglobulins and macroglobulins were negative. The thymol turbidity test and cephalin-cholesterol reaction were normal. Blood serum glucose was 58 mg. per 100 ml., urea 23 mg. per 100 ml., bilirubin 1 mg. per 100 ml. The serum iron was found to be 10 gamma per 100 ml.

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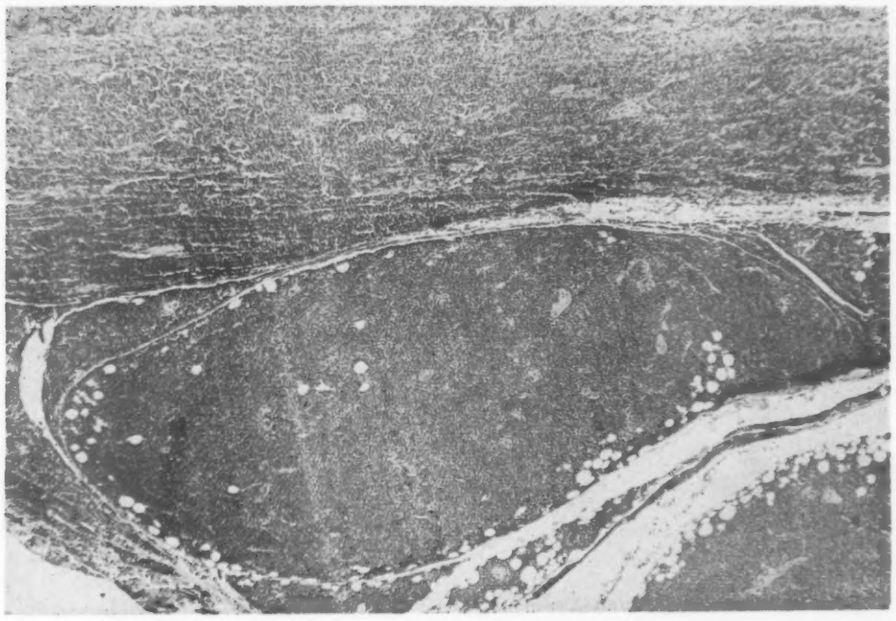

FIG. 1. Axillary lymph node: malignant lymphoma, lymphocytic type. There is complete obliteration of normal architecture with uniform proliferation of small lymphocytes infiltrating capsule and pericapsular fat tissue. Hematoxylin and eosin; original magnification, × 160.

Kahn and Kline tests for syphilis were negative. Urinalysis showed occasional traces of protein. Repeated tests for Bence Jones protein were negative.

Sternal marrow, both in smears and sections, showed a marked increase in the number of lymphocytes, the majority of which appeared completely mature. Reticulum cells were more numerous than normally.

A biopsy of an axillary lymph node showed normal architecture obliterated by closely packed uniform cells of the lymphocytic series. The lymphocytes were mostly mature and massively infiltrated the capsule and the perinodal tissue. Hemosiderin-laden macrophages and erythrophagocytosis were observed in compressed sinuses. The pathologic diagnosis was malignant lymphoma, lymphocytic type, well differentiated, consistent with chronic lymphocytic leukemia. (Figs. 1 and 2.)

A skin biopsy from the axilla revealed a uniform lymphocytic infiltration of the dermis, particularly around the cutaneous appendages and blood vessels. These findings were interpreted as indicative of lymphocytic leukemia cutis. Moderately severe bleeding from the surgical incision occurred after the biopsy.

The pleural fluid withdrawn from the right pleural cavity was milky and brownish yellow in color. The specific gravity was 1.020. Rivalta's test was positive. The fluid clotted on standing. The total protein was 5.6 gm. per 100 ml. Paper electrophoresis revealed the following distribution: albumin 1.9 gm., alpha globulin 0.6 gm., beta globulin 0.3 gm., gamma globulin 2.8 gm. per 100 ml. Cytologic examination of the sediment disclosed mature lymphocytes. The milky appearance of the fluid was only partially cleared up by ether extraction.

The patient's blood group was O rh (cde). No warm autoagglutinins were found at 37°c. using the patient's own and other group O red cells suspended in saline solution and serum albumin, as well as papain-treated cells. Cold agglutinins were present and appeared to be of the immune type; the titer was 1:4 in saline solution, 1:228 in serum albumin and 1:512 with papain-treated cells. No significant difference was found using the patient's own cells, and other cells of group O, Rh-positive and Rh-negative. The isoagglutinin titer (anti-A and anti-B) was 1:5. Agglutinins for sheep red cells were present in a titer of 1:5. Cold hemolysins and acid hemolysins for the patient's own and for other O cells and hemolysins for sheep red cells were not found.

The diagnosis of chronic lymphocytic leukemia was made on the basis of the lymph node, skin and marrow biopsies. The age of the patient, the slow onset, the symmetric distribution of the enlarged lymph nodes, fitted with the usual picture of the disease. Radiotherapy was thought to be indicated by the generalized lymph node and skin involvement. Spray radiation was started and repeated small blood transfusions were given. The itching was greatly relieved immediately after the first treatment and the petechiae disappeared gradually.

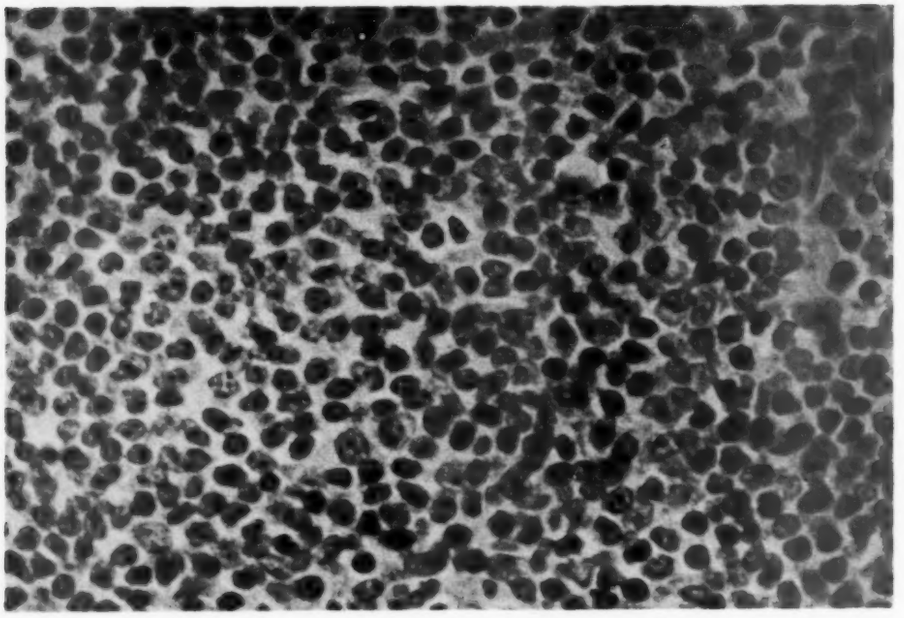

FIG. 2. Same as in Figure 1. The lymphocytes are well differentiated and cytologically characteristic of chronic lymphocytic leukemia. Hematoxylin and eosin; original magnification, × 1,600.

Follow-up of the patient after six months showed marked improvement, both subjectively and according to the blood count (red blood cells 3,720,000 per cu. mm., hemoglobin 11.6 gm. per cent, white blood cells 7,500 per cu. mm., with an essentially normal differential count). A second electrophoretic analysis of the serum proteins revealed the following pattern: total protein 10.7 gm., albumin 2.9 gm., globulin 7.8 gm., alpha globulin 0.9 gm., beta globulin 0.6 gm., gamma globulin 6.3 gm. per 100 ml.

EXPERIMENTAL DATA

In order to determine whether the increased serum gamma globulins might be derived from the neoplastic (leukemic) tissue, an extract was prepared from one of the axillary lymph nodes, according to the technic of Abrams et al. [*3,4*]. The lymph node was cleared as much as possible of its adipose and connective tissue and cut into minute pieces that were washed by repeated centrifugation and resuspension in equal parts of 0.07 molar potassium bicarbonate and 0.07 molar potassium chloride at approximately pH 8. The washed tissue was then homogenized with an equal amount of the same salt solution and centrifuged for two hours at 3,000 r.p.m. The operation was carried out in the cold room at 4°C. A pink viscous fluid was obtained. Microscopic examination failed to reveal any nuclear remnants. According to Abrams, only insignificant amounts of nuclear proteins are demonstrable in the supernatant fluid prepared by this technic.

The supernatant fluid (0.01 ml.) was analyzed by means of paper electrophoresis. The experiment was carried on for eighteen hours at 5 MA using a barbiturate buffer solution at pH 8.6. A high sharp peak was noted in the area of the gamma globulins and smaller amounts of fractions with faster motility were also noted. (Fig. 3.)

In order to determine whether or not we were dealing with a specific pattern, we investigated a small number of lymph nodes, including a normal lymph node, as well as lymph nodes from patients with chronic lymphocytic leukemia, chronic granulocytic leukemia, lymphosarcoma and reticulum cell sarcoma. In all of them we found a pattern characterized by a prominent peak in the area of the gamma globulins, with smaller amounts of fractions showing faster motility. (Fig. 4.) While the highest peak was found in the lymph node extract of the patient under discussion, the value obtained from a lymph node of another patient with chronic lymphocytic leukemia without demonstrable abnormal serum proteins was almost as high.

A closer relationship between the abnormal proteins and the leukemic tissue would have been suggested by the demonstration in the

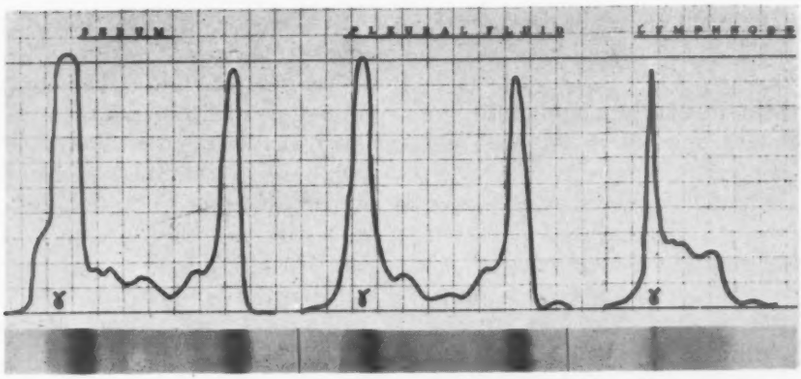

FIG. 3. Electrophoretic pattern of serum, pleural fluid and lymph node extract.

lymph node extract of the same antibodies found in the serum and by the localization of these antibodies in the increased gamma globulin fraction. We tested the lymph node extract for hemagglutinins, using untreated and papain-treated red cells, as well as the indirect Coombs' test, but we were not able to detect cold or other agglutinins. An attempt to isolate the antibodies from each of the electrophoretic fractions of the serum of the patient according to the technic of Payne [*5*] was also unsuccessful. A relatively low titer and the extremely small amount of protein employed in paper electrophoresis may have accounted for this failure.

An additional investigation was carried out in order to study the mechanism of the anemia. The survival of the red cells of the patient was determined with the radiochromium technic [*6*] and found to be definitely shortened. Fifty per cent of the cells tagged with Cr^{51} disappeared within fifteen days, whereas the normal half-life with this technic should be approximately thirty days.

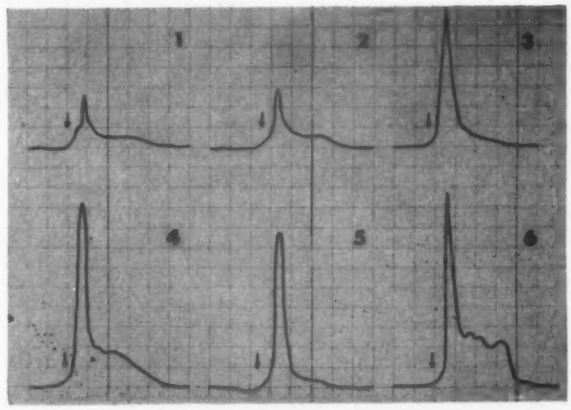

FIG. 4. Comparison of electrophoretic pattern of lymph node extract of patient reported herein with lymph node extracts from five other individuals: (1) normal lymph node, (2) lymphosarcoma, (3) chronic granulocytic leukemia, (4) chronic lymphocytic leukemia, (5) reticulum cell sarcoma, (6) present case.

COMMENTS

Four points are of special interest in this case: (1) the abnormalities of the plasma proteins, (2) the presence of cold agglutinins, (3) the mechanism of the anemia, and (4) the hemorrhagic manifestations.

Quantitative and qualitative alterations of serum proteins in chronic lymphocytic leukemia have been reported in the past, using either chemical methods or electrophoresis. The results did not show a consistent pattern. Normal or subnormal values of serum proteins have been recorded [*2,7–11*], as well as slight increase of gamma globulin often associated with hypoalbuminemia [*12–15*]. Only rare instances of extreme elevation of gamma globulin are on record. In a case of Rundles [*2*], the total proteins were 12.8 gm. per cent and the gamma globulin 7.8. In a case of Beyreder [*8*], the total proteins were 8.6 gm. per cent and the gamma globulins accounted for 56.2 per cent of the total protein.

An analysis of one of the largest series of cases [*2*] suggests that in typical cases of chronic lymphocytic leukemia with mild or no constitutional symptoms, no significant blood protein changes have been noted but that in seriously ill patients or those with subleukemic or aleukemic forms of the disease, an increase of gamma globulin is more likely to occur. In the same report, abnormal fractions with electrophoretic motility between that of the beta and of gamma globulins have been described in a few cases. The concentration of the abnormal fractions seemed

to be related to the clinical course of the disease, since they diminished as the patient's condition improved under therapy.

The problem of the site of origin of globulins in normal and pathologic conditions has been the subject of much study. In experiments in mice and rabbits, White and Dougherty [*16,17*] were able to demonstrate in saline extracts prepared from lymph nodes a reproducible pattern of four fractions, two of which had mobilities comparable to those of the plasma beta and gamma globulins. After treatment with ACTH, peculiar cellular alterations such as budding and shedding of the lymphocyte cytoplasm were associated with an increase of the plasma gamma and beta globulins, suggesting the possibility of release of the globulins from the disintegrating lymphocytes. Using a slightly lower pH, Roberts and White [*18*] could isolate six to eight components in lymph nodes from rabbits and in mouse lymphosarcoma. Gamma globulins were also identified in human lymphocytes obtained from lymphoid tissues by means of immunologic methods [*19*]. Indirect evidence to suggest a possible relationship between lymphocytes and gamma globulins is furnished by the observation that in widespread destruction of lymphoid tissue by radiation or nitrogen mustard, low values of gamma globulins are found [*20*]. It is worthy of note that in some patients with agammaglobulinemia and hypogammaglobulinemia, decreased amounts of peripheral lymphocytes and hypoplasia of the lymphoid tissue have been found [*21,22*].

The suggestion that the tissue of malignant lymphoma may be the site of origin of abnormal proteins and possibly of antibodies in patients with acquired hemolytic anemia was based primarily upon clinical observations, including the effects of ACTH, that simultaneously produced decrease in the autoagglutinin titer and in the number of circulating lymphocytes, regression of lymph nodes and clinical improvement [*23,24*]. More direct evidence in support of formation of abnormal proteins by lymphoma tissue was furnished recently. Abrams et al. [*4*] extracted a cryoglobulin from a lymph node of a patient with lymphosarcoma. This abnormal globulin had properties identical with those of a cryoglobulin in the patient's serum. More recently, intracellular proteins, morphologically and histochemically resembling Russell bodies, were demonstrated in neoplastic lymphocytes of patients with malignant lymphoma [*25*].

In our case the fraction responsible for the hyperproteinemia consisted of gamma globulins with normal mobility. The albumin fraction was only slightly decreased. A similar pattern was also observed in the pleural fluid, whereas the lymph node extract was almost entirely composed of gamma globulin. This suggests that the high gamma globulin content of the tissue extract was not due to contamination by blood [*4*] but that the proliferating leukemia lymphocytes may have been the source of gamma globulins in the lymph node tissue. It is conceivable that the increase of circulating gamma globulins was also related to the excessive proliferation of well differentiated leukemic lymphocytes.

Acquired hemolytic anemia has been reported in many instances of chronic lymphocytic leukemia [*23–29*]. The clinical picture may vary from a mild hemolytic state, detectable only by special methods, to severe hemolytic crisis. In many instances autoimmunization was present, the patient's erythrocytes giving a positive direct Coombs' test. In some cases autoantibodies of the warm or cold type have been demonstrated in the patient's serum. The frequency with which autoimmunization may be detected in patients who have chronic lymphocytic leukemia associated with hemolytic anemia depends to some extent on the sensitivity of the technics used for detection of the antibodies. A consistent relationship between the presence of abnormal proteins and of immune antibodies has not been established, even though the two often are found together [*24–26*].

While we were unable to demonstrate antibodies in the lymph node extract of our patient, recent observations suggest that neoplastic cells of malignant lymphomas may be a source of autoantibodies in some patients. Aubert and Brendemoen [*30*] demonstrated cold agglutinins in warm saline washings of tumor tissue. A similar observation was made more recently by Wiener et al. [*31*] in a case of lymphosarcoma.

The final feature to be considered is the hemorrhagic tendency manifested by our patient. This may, at least in part, be related to the existing hyperglobulinemia. Cases of purpura characterized by high levels of normal globulin, or by the presence of atypical proteins, have been described [*32–34*]. Other observers have demonstrated that increases in various globulin fractions were associated with a disturbance of conversion of fibrinogen to fibrin [*35–37*], presumably due to a specific anticoagulant action

[*38*]. This may have accounted for the prolonged prothrombin time in our patient, although other factors, such as deficient formation of prothrombin, or of stable or labile factors, could not be excluded.

SUMMARY

An unusual case of chronic aleukemic lymphocytic leukemia with dysproteinemia and acquired hemolytic anemia is presented. Significant features included: (1) hyperproteinemia with marked increase of gamma globulins, (2) presence of cold agglutinins of the immune type, (3) decreased red cell survival and (4) abnormal bleeding tendency. Electrophoretic analysis of a lymph node extract revealed a high peak in the area of the gamma globulins corresponding to similar elevations in the serum and in the pleural fluid of the patient. These findings indicate a high concentration of gamma globulin in the leukemic tissue of the patient and suggest that not only normal but also leukemic lymphocytes may be the source of gamma globulins.

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